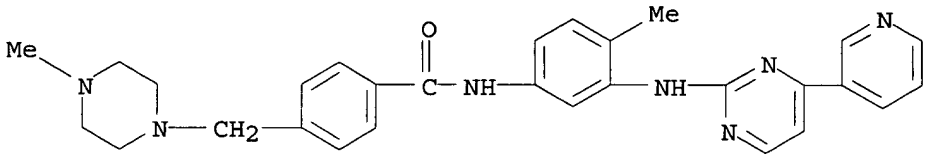
=> s Gleevec/cn

L1 1 GLEEVEC/CN

=> d l1

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2001 ACS
RN 152459-95-5 REGISTRY
CN Benzamide, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN CGP 57148
CN CGP 57148B
CN Gleevac
CN **Gleevec**
CN Glivec
CN Imatinib
CN STI 571
MF C29 H31 N7 O
CI COM
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, BIOSIS, BIOTECHNO, CA, CAPLUS, CIN, DDFU, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, PHAR, PROMT, SYNTHLINE, TOXLIT, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

61 REFERENCES IN FILE CA (1967 TO DATE)
62 REFERENCES IN FILE CAPLUS (1967 TO DATE)

=> d prop

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2001 ACS

Calculated Properties (CALC)

CODE	PROPERTY	VALUE	CONDITION	NOTE
HD	H donors	2		ACD (1)
HAC	H acceptors	8		ACD (1)
MW	Molecular Weight	493.60		ACD (1)
LOGP	logP	1.861+/-0.664		ACD (1)

LOGD	logD	-4.16	pH 1	ACD (1)
LOGD	logD	-1.17	pH 4	ACD (1)
LOGD	logD	1.18	pH 7	ACD (1)
LOGD	logD	1.72	pH 8	ACD (1)
LOGD	logD	1.86	pH 10	ACD (1)
PKA	pKa	13.28+/-0.70	Most Acidic	ACD (1)
PKA	pKa	7.53+/-0.30	Most Basic	ACD (1)
SLB.MOL	Molar Solubility	>=1 mol/L	pH 1	ACD (1)
SLB.MOL	Molar Solubility	>=0.01 - <0.1 mol/L	pH 4	ACD (1)
SLB.MOL	Molar Solubility	<0.01 mol/L	pH 7	ACD (1)
SLB.MOL	Molar Solubility	<0.01 mol/L	pH 8	ACD (1)
SLB.MOL	Molar Solubility	<0.01 mol/L	pH 10	ACD (1)

(1) Calculated using Advanced Chemistry Development (ACD) Software Solaris V4.67 ((C) 1994-2001 ACD)

=> s 152459-95-5/crn

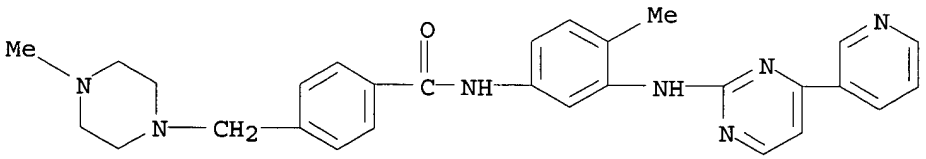
L2 1 152459-95-5/CRN

=> d 12

L2 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2001 ACS
RN 220127-57-1 REGISTRY
CN Benzamide, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-, monomethanesulfonate (9CI) (CA INDEX NAME)
MF C29 H31 N7 O . C H4 O3 S
SR CA
LC STN Files: CA, CAPLUS, SYNTHLINE, TOXLIT

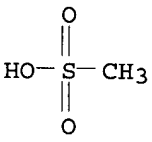
CM 1

CRN 152459-95-5
CMF C29 H31 N7 O



CM 2

CRN 75-75-2
CMF C H4 O3 S



2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

=> file caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	9.66	10.11

FILE 'CAPLUS' ENTERED AT 12:17:05 ON 19 OCT 2001
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FILE COVERS 1947 - 19 Oct 2001 VOL 135 ISS 18
FILE LAST UPDATED: 18 Oct 2001 (20011018/ED)

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The CA Lexicon is now available in the Controlled Term (/CT) field. Enter HELP LEXICON for full details.

=> s l2

L3 2 L2

=> d 1-2 bib abs

L3 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2001 ACS
AN 2001:661241 CAPLUS
DN 135:221308
TI Use of PDGF receptor tyrosine kinase inhibitors for the treatment of diabetic nephropathy
IN Atkins, Robert Charles; Chadban, Steven James; Cooper, Mark Emmanuel; Gilbert, Richard Ernest; Hill, Prudence Ann; Kelly, Darren James; Nikolic-Paterson, David John
PA Novartis A.-G., Switz.; The University of Melbourne; Southern Health
SO PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001064200	A2	20010907	WO 2001-EP2340	20010301

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI EP 2000-810181 A 20000303

OS MARPAT 135:221308

AB The present invention relates to the use of PDGF receptor tyrosine kinase inhibitors, esp. N-phenyl-2-pyrimidineamine derivs. for the treatment of diabetic nephropathy, glomerulonephritis, chronic pyelonephritis or IgA nephropathy. Thus, CGP 57148B administered in gum arabic as an oral suspension to rats, the left kidney of which was removed, was shown to inhibit the diorder.

L3 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2001 ACS

AN 1999:77563 CAPLUS

DN 130:158400

TI Crystal modification of a N-phenyl-2-pyrimidineamine derivative, processes for its manufacture and its use

IN Zimmermann, Jurg; Sutter, Bertrand; Burger, Hans Michael

PA Novartis A.-G., Switz.; Novartis-Erfindungen Verwaltungsgesellschaft m.b.H.

SO PCT Int. Appl., 30 pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9903854	A1	19990128	WO 1998-EP4427	19980716

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

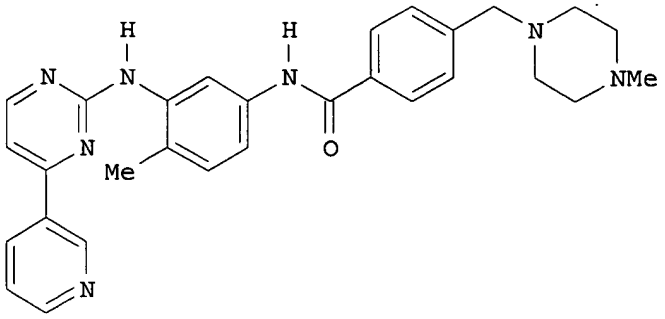
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

	AU 9889759	A1	19990210	AU 1998-89759	19980716
	EP 998473	A1	20000510	EP 1998-941342	19980716

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO

	BR 9810920	A	20000815	BR 1998-10920	19980716
	JP 2001510192	T2	20010731	JP 2000-503078	19980716
	ZA 9806362	A	19990122	ZA 1998-6362	19980717
	NO 2000000227	A	20000117	NO 2000-227	20000117
PRAI	CH 1997-1764	A	19970718		
	WO 1998-EP4427	W	19980716		

GI



I

AB The invention relates to a new cryst. form of the methanesulfonic acid addn. salt of I which may be used, for example, for tumor therapy. I was treated with methanesulfonic acid in MeOH to give the .alpha.-crystal form which in MeOH soln. is inoculated with a .beta.-crystal form to give the .beta.-variants. Tablets and capsules were prepd. contg. these crystal forms.

RE.CNT 1

RE

(1) Zimmermann, J; US 5521184 A 1996 CAPLUS

```
=> d his

     (FILE 'HOME' ENTERED AT 16:06:39 ON 22 OCT 2001)

     FILE 'MEDLINE' ENTERED AT 16:06:45 ON 22 OCT 2001
L1          4724 S (BCR-ABL) OR (C-KIT)
L2           670 S L1 AND REVIEW?/DT
L3            30 S (BCR-ABL) AND (C-KIT)
```

=> d l2 400 500 600 bib abs

L2 ANSWER 400 OF 670 MEDLINE
AN 95346988 MEDLINE
DN 95346988 PubMed ID: 7621511
TI Inhibition of gene expression with ribozymes.
AU Marschall P; Thomson J B; Eckstein F
CS Max-Planck-Institut fur Experimentelle Medizin, Gottingen, Germany.
SO CELLULAR AND MOLECULAR NEUROBIOLOGY, (1994 Oct) 14 (5) 523-38. Ref: 79
Journal code: CPX; 8200709. ISSN: 0272-4340.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199508
ED Entered STN: 19950911
Last Updated on STN: 19970203
Entered Medline: 19950830
AB 1. Ribozymes can be designed to cleave in trans, i.e. several substrate molecules can be turned over by one molecule of the catalytic RNA. Only small molecular weight ribozymes, or small ribozymes, are discussed in this review with particular emphasis on the hammerhead ribozyme as this has been most widely used for the inhibition of gene expression by cleavage of mRNAs. 2. Cellular delivery of the ribozyme is of crucial importance for the success of inhibition of gene expression by this methodology. Two modes of delivery can be envisaged, endogenous and exogenous delivery. Of the former several variants exist, depending on the vector used. The latter is still in its infancy, even though chemical modification has rendered such ribozymes resistant against degradation by serum nucleases without impairment of catalytic efficiency. 3. Various successful applications of ribozymes for the inhibition of gene expression are discussed, with particular emphasis on HIV1 and cancer targets. These examples demonstrate the promise of this methodology.

L2 ANSWER 500 OF 670 MEDLINE
AN 94107978 MEDLINE
DN 94107978 PubMed ID: 7506582
TI Hypergranular acute lymphoblastic leukemia (ALL). Report of a case and review of the literature.
AU Schwarzinger I; Fodinger M; Scherrer R; Wolzt M; Mannhalter C; Speiser W
CS Clinical Institute for Medical, University of Vienna, Austria.
SO ANNALS OF HEMATOLOGY, (1993 Dec) 67 (6) 301-3. Ref: 21
Journal code: A2P; 9107334. ISSN: 0939-5555.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199402
ED Entered STN: 19940228

Last Updated on STN: 19960129
Entered Medline: 19940217

AB We report a case of adult acute lymphoblastic leukemia (ALL) with myeloid-like hypergranulation of blast cells. Like most of the "granular" ALLs described in the literature, the blast cells had L2 morphology and exhibited a common-ALL immunologic phenotype. The clinical findings at diagnosis were unremarkable. Cytogenetic analysis showed a 46XY karyotype.

Molecular genetic analysis revealed T-cell receptor (TCR) gamma and immunoglobulin heavy chain rearrangements; no rearrangement was found at the TCR beta gene locus. The polymerase chain reaction (PCR) for the **BCR-ABL** translocation was negative. The clinical course of the patient was uncomplicated. On standard ALL treatment protocol he achieved complete remission (CR) within 4 weeks, and he is currently disease free 8 months after diagnosis. The case contributes well-documented data to the characterization of adult "granular" ALL, with special regard to changes at the molecular genetic level.

L2 ANSWER 600 OF 670 MEDLINE
AN 92265326 MEDLINE
DN 92265326 PubMed ID: 1726043
TI The kit ligand encoded at the murine Steel locus: a pleiotropic growth and differentiation factor.
AU Besmer P
CS Sloan Kettering Institute, New York.
SO CURRENT OPINION IN CELL BIOLOGY, (1991 Dec) 3 (6) 939-46. Ref: 50
Journal code: AOE; 8913428. ISSN: 0955-0674.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199206
ED Entered STN: 19920710
Last Updated on STN: 20000303
Entered Medline: 19920622

AB The **c-kit** receptor and its recently identified ligand are allelic with the murine White Spotting and Steel loci, respectively. These observations brought to light the functions of the **c-kit** receptor system in melanogenesis, gametogenesis and hematopoeisis during embryogenesis and in postnatal life. The recent molecular analysis of several White Spotting and Steel alleles has provided insights into the mechanism of **c-kit** ligand-mediated processes, including cell proliferation, cell migration and cell survival. Furthermore, the availability of the kit ligand has allowed in vitro investigations of the pleiotropic functions of **c-kit** in development and cell differentiation to be carried out.

=> d his

(FILE 'HOME' ENTERED AT 16:06:39 ON 22 OCT 2001)

FILE 'MEDLINE' ENTERED AT 16:06:45 ON 22 OCT 2001
L1 4724 S (BCR-ABL) OR (C-KIT)
L2 670 S L1 AND REVIEW?/DT

=> S (BCR-ABL) and (C-KIT)

3764 BCR

```
          3993 ABL
          2292 BCR-ABL
                 (BCR(W)ABL)
        683543 C
         10223 KIT
          2462 C-KIT
                 (C(W)KIT)
L3          30 (BCR-ABL) AND (C-KIT)

=> d bro

:*kwic

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L3   ANSWER 1 OF 30     MEDLINE
AB   . . . for therapeutic intervention. Chronic myelogenous leukemia (CML)
     represents an ideal target for a therapy using a selective inhibitor of
     the BCR-ABL tyrosine kinase. The 2-phenylpyrimidine
     derivative STI571 was rationally designed to inhibit ABL and BCR
     -ABL tyrosine kinase activities through competitive ATP-binding
     pocket interactions. Phase II data demonstrate hematologic and
cytogenetic
     responses in interferon refractory chronic-phase,. . . prolongation of
     survival. STI571 is being studied in other malignancies, including
     leukemias characterized by expression of alternate molecular forms of
     BCR-ABL and those expressing protein tyrosine kinases
     with ATP-binding pockets structurally similar to ABL, e.g. c-
     kit and PDGF-R. Gastrointestinal stromal tumor (GIST) cells
     overexpress the stem cell factor receptor CD117, the product of the
     proto-oncogene c-kit. Inhibition of c-
     kit in vivo results in an immediate metabolic change of the tumor
     cells, detectable by positron emission tomography. Since c-
     kit overexpression is inhibited in small-cell lung cancer cell
     lines, a study with STI571 as second-line therapy of c-
     kit-positive small-cell lung cancer is in progress. Clinical
     studies are ongoing in malignancies associated with an enhanced activity
     of the PDGF-R,. . .
:.


L3   ANSWER 2 OF 30     MEDLINE
AB   The tyrosine kinase inhibitor imatinib (STI571, Glivec) blocks the
     activity of the BCR/ABL oncogene and induces
     hematologic remissions in the majority of patients with chronic myeloid
     leukemia (CML). Glivec is an aminopyrimidine derivative that interacts
     with the ATP-binding site within the kinase domain of ABL and several
     other tyrosine kinases, including c-KIT, PDGF beta
     receptor, and ARG. The compound is currently in phase III clinical
trials.
     Although patients with chronic phase CML. . .
:.


L3   ANSWER 3 OF 30     MEDLINE
AB   . . . stem cell disorder, is characterised by an acquired genetic
     abnormality: the Philadelphia chromosome (Ph) and its molecular
     counterpart, the oncogene BCR-ABL. The latter, which
     is translated in an active BCR-ABL protein, exhibited
     a deregulated tyrosine kinase activity inducing malignant transformation.
     Produced from the 2-phenylaminopyrimidine class, a novel synthetic
     inhibitor, identified as CGP57148 (STI571), inhibits tyrosine kinase
     activity of c-ABL, BCR-ABL, PDGF-R and c-
```

kit at micromolar concentrations. It suppresses the proliferation of the majority of **BCR-ABL** positive cell lines. The phases I-II clinical trials in CML have demonstrated promising results, especially in the chronic phase of. . .

:.

L3 ANSWER 4 OF 30 MEDLINE
AB . . . difference in oncogene expression could be observed in LTBMC from
CML patients regarding reduction of Philadelphia chromosome-associated transcription of the **BCR-ABL** gene. With respect to the expression of growth and differentiation-associated genes (Galpha16, 5-lipoxygenase, phospholipaseA2, **c-kit**, and CD34), which were analyzed from LTBMC by semiquantitative reverse transcriptase-polymerase chain reaction, the same transcription rate was observed in. . .

:.

L3 ANSWER 5 OF 30 MEDLINE
AB . . . agent (an agent whose anti-cancer activity is not predicated on a
cytotoxic mechanism). STI-571 has already shown clinical value in **BCR-ABL**-positive leukemias. Early clinical results in GIST are so encouraging that oncologists may soon be wrestling with the opportunity of referring. . .
CT . . .
therapy
Gastrointestinal Neoplasms: GE, genetics
Gastrointestinal Neoplasms: PA, pathology
Piperazines: TU, therapeutic use
Prognosis
Protein-Tyrosine Kinase: AI, antagonists & inhibitors
Proto-Oncogene Protein c-kit: AN, analysis
Pyrimidines: TU, therapeutic use
*Stromal Cells
CN 0 (CGP 57148); 0 (Enzyme Inhibitors); 0 (Piperazines); 0 (Pyrimidines);
EC
2.7.1.112 (Protein-Tyrosine Kinase); EC 2.7.11.- (Proto-Oncogene Protein **c-kit**)

:.

L3 ANSWER 6 OF 30 MEDLINE
TI STI571: targeting **BCR-ABL** as therapy for CML.
AB . . . agent STI571 (signal transduction inhibitor number 571) is a rationally developed, potent, and selective inhibitor for abl tyrosine kinases, including **bcr-abl**, as well **c-kit** and the platelet-derived growth factor receptor tyrosine kinases. Results of clinical trials to date have demonstrated the crucial role of the **bcr-abl** tyrosine kinase in chronic myelogenous leukemia (CML) pathogenesis and the potential of anticancer agents designed to target specific molecular abnormalities. . .

:.

L3 ANSWER 7 OF 30 MEDLINE
AB The tyrosine kinase inhibitor STI571 inhibits **BCR/ABL** and induces hematologic remission in most patients with chronic myeloid leukemia. In addition to **BCR/ABL**, STI571 also inhibits v-Abl, TEL/ABL, the native platelet-derived growth factor (PDGF)beta receptor, and **c-KIT**, but it does not inhibit SRC family kinases, c-FMS, FLT3, the epidermal growth factor receptor, or

multiple other tyrosine kinases.. . . increased tyrosine phosphorylation of multiple cellular proteins, and induced factor-independent proliferation. The effects of STI571 on Ba/F3 cells transformed with **BCR/ABL**, TEL/ABL, TEL/PDGFbetaR, or TEL/ARG were then compared. STI571 inhibited tyrosine phosphorylation and cell growth of Ba/F3 cells expressing **BCR/ABL**, TEL/ABL, TEL/PDGFbetaR, and TEL/ARG with an IC(50) of approximately 0.5 microM in each case, but it had no effect on. . . of TEL/ARG-transfected Ba/F3 cells with IL-3 completely prevented STI571-induced apoptosis in these cells, similar to what has been observed with **BCR/ABL**- or TEL/ABL-transformed cells. These results indicate that ARG is a target of the small molecule, tyrosine kinase inhibitor STI571.

CT . . .
enzymology
Cell Transformation, Neoplastic: DE, drug effects
Cell Transformation, Neoplastic: GE, genetics
DNA, Complementary: GE, genetics
*Enzyme Inhibitors: PD, pharmacology
Fusion Proteins, bcr-abl: GE, genetics
Fusion Proteins, bcr-abl: PH, physiology
Hematopoietic Stem Cells: DE, drug effects
Mice
Molecular Sequence Data
Neoplasm Proteins: GE, genetics
Neoplasm. . .

CN 0 (CGP 57148); 0 (DNA, Complementary); 0 (Enzyme Inhibitors); 0 (Fusion Proteins, **bcr-abl**); 0 (Neoplasm Proteins); 0 (Oncogene Proteins, Fusion); 0 (Piperazines); 0 (Pyrimidines); 0 (TEL-ABL fusion protein); 0 (TEL-ARG fusion protein); 0. . .

:.

L3 ANSWER 8 OF 30 MEDLINE

TI Abl protein-tyrosine kinase inhibitor STI571 inhibits in vitro signal transduction mediated by **c-kit** and platelet-derived growth factor receptors.

AB . . . the Abl and platelet-derived growth factor (PDGF) receptor tyrosine kinases in vitro and blocks cellular proliferation and tumor growth of **Bcr-abl**- or v-abl-expressing cells. We have further investigated the profile of STI571 against related receptor tyrosine kinases. STI571 was found to. . . addition to chronic myelogenous leukemia, STI571 may have clinical potential in the treatment of diseases that involve abnormal activation of **c-Kit** or PDGF receptor tyrosine kinases.

CT . . . Animal
*Antineoplastic Agents: PD, pharmacology
Cell Line
*Enzyme Inhibitors: PD, pharmacology
Mice
Mitogen-Activated Protein Kinases: PH, physiology
*Piperazines: PD, pharmacology
***Proto-Oncogene Protein c-kit: DE, drug effects**
Proto-Oncogene Protein c-kit: PH, physiology
*Proto-Oncogene Proteins c-abl: AI, antagonists & inhibitors
*Pyrimidines: PD, pharmacology
*Receptors, Platelet-Derived Growth Factor: AI,. . .

CN. . . (Piperazines); 0 (Proto-Oncogene Proteins c-abl); 0 (Pyrimidines); 0 (Stem Cell Factor); EC 2.7.1.- (Mitogen-Activated Protein Kinases); EC 2.7.11.- (Proto-Oncogene Protein **c-kit**); EC 2.7.11.- (Receptors, Platelet-Derived Growth Factor)

:.

L3 ANSWER 9 OF 30 MEDLINE
AB . . . from patients with myeloproliferative disorders show variable proliferative response to SCF as the sole mitogenic stimulus, suggesting that expression of **bcr-abl** is essential for proliferation in this cytokine. Further studies to identify the key determinants of the abnormal response to SCF. . .
CT . . .
Apoptosis
Autocrine Communication
Cell Adhesion: DE, drug effects
Cell Division: DE, drug effects
Extracellular Matrix: ME, metabolism
Fibronectins: ME, metabolism
Fusion Proteins, bcr-abl: PH, physiology
*Hematopoietic Stem Cells: DE, drug effects
Hematopoietic Stem Cells: PA, pathology
*Leukemia, Myeloid, Philadelphia-Positive: PA,. . . Ligands
Neoplasm Proteins: DE, drug effects
Neoplasm Proteins: GE, genetics
Neoplasm Proteins: PH, physiology
Phosphorylation
Protein Processing, Post-Translational: GE, genetics
Proto-Oncogene Protein c-kit: DE, drug effects
Proto-Oncogene Protein c-kit: GE, genetics
Proto-Oncogene Protein c-kit: PH, physiology
Recombinant Fusion Proteins: PH, physiology
*Stem Cell Factor: PD, pharmacology
Transfection
Tumor Cells, Cultured: DE,. . .
CN 0 (Fibronectins); 0 (Fusion Proteins, **bcr-abl**); 0 (Ligands); 0 (Neoplasm Proteins); 0 (Recombinant Fusion Proteins); 0 (Stem Cell Factor); EC 2.7.11.- (Proto-Oncogene Protein **c-kit**)
:.

L3 ANSWER 10 OF 30 MEDLINE
AB . . . lung cancer (SCLC) is an aggressive cancer characterized by several autocrine growth mechanisms including stem cell factor and its receptor **c-Kit**. In order to arrive at potentially new and novel therapy for SCLC, we have investigated the effects of the tyrosine. . . previously reported that STI 571 does not only inhibit cellular Abl tyrosine kinase activity but also the PDGF receptor and **c-Kit** tyrosine kinases at similar concentrations (approximately 0.1 microM). There is no expression of the PDGF-receptor, and the Abl kinase is not activated by SCLC, but over 70% of SCLC contain the **c-Kit** receptor. Utilizing this preliminary data, we have determined that three (NCI-H69, NCI-H146 and NCI-H209) of five (including NCI-H82 and NCI-H249) SCLC cell lines had detectable **c-Kit** receptors and were inhibited in growth and viability at concentrations 1 - 5 microM of STI 571 after 48 h. . . cell lines, NCI-H69, NCI-H146 and NCI-H209, showed a dose-response (tested between 0.1 - 10 microM) inhibition of tyrosine phosphorylation of **c-Kit** as well as in vitro kinase activity (at 5 microM) of **c-Kit** in response to STI 571. STI 571 inhibited cell motility, as assessed by time-lapsed video microscopy, within 6 h of. . . that cells were generally slowed in G2/M phase, but there was no arrest at G1/S. A downstream phosphorylation target of **c-Kit**, Akt, was not phosphorylated in response to stem cell factor in the presence of STI

571. These data imply that STI 571 inhibits growth of SCLC cells through a mechanism that involves inactivation of the tyrosine kinase **c-Kit**. The effectiveness of STI 571 in this study suggests this drug may be useful in a clinical trial, for patients. . .

CT . . .
Sulfoxide: PD, pharmacology
Dose-Response Relationship, Drug
Drug Screening Assays, Antitumor
Enzyme Inhibitors: AD, administration & dosage
*Enzyme Inhibitors: PD, pharmacology
Fusion Proteins, bcr-abl: AI, antagonists & inhibitors
Growth Inhibitors: AD, administration & dosage
*Growth Inhibitors: PD, pharmacology
Hematopoietic Stem Cells:. . . PH, physiology
Phosphorylation
Piperazines: AD, administration & dosage
*Piperazines: PD, pharmacology
Protein Processing, Post-Translational
*Protein-Tyrosine Kinase: AI, antagonists & inhibitors
***Proto-Oncogene Protein c-kit: PH, physiology**
Proto-Oncogene Proteins: ME, metabolism
Pyrimidines: AD, administration & dosage
*Pyrimidines: PD, pharmacology
Reactive Oxygen Species
Tumor. . .

CN 0 (Antineoplastic Agents); 0 (CGP 57148); 0 (Enzyme Inhibitors); 0 (Fusion Proteins, **bcr-abl**); 0 (Growth Inhibitors); 0 (Neoplasm Proteins); 0 (Piperazines); 0 (Proto-Oncogene Proteins); 0 (Pyrimidines); 0 (Reactive Oxygen Species); 0 (proto-oncogene protein akt); EC 2.7.1.112 (Protein-Tyrosine Kinase); EC 2.7.11.- (Proto-Oncogene Protein **c-kit**)
:.

L3 ANSWER 11 OF 30 MEDLINE
TI Inhibition of **c-kit** receptor tyrosine kinase activity by STI 571, a selective tyrosine kinase inhibitor.
AB STI 571 (formerly known as CGP 57148B) is a known inhibitor of the c-abl, **bcr-abl**, and platelet-derived growth-factor receptor (PDGFR) tyrosine kinases. This compound is being evaluated in clinical trials for the treatment of chronic. . . sought to extend the activity profile of STI 571 by testing its ability to inhibit the tyrosine kinase activity of **c-kit**, a receptor structurally similar to PDGFR. We treated a **c-kit** expressing a human myeloid leukemia cell line, M-07e, with STI 571 before stimulation with Steel factor (SLF). STI 571 inhibited **c-kit** autophosphorylation, activation of mitogen-activated protein (MAP) kinase, and activation of Akt without altering total protein levels of **c-kit**, MAP kinase, or Akt. The concentration that produced 50% inhibition for these effects was approximately 100 nmol/L. STI 571 also. . . activity of STI 571 in a human mast cell leukemia cell line (HMC-1), which has an activated mutant form of **c-kit**. STI 571 had a more potent inhibitory effect on the kinase activity of this mutant receptor than it did on ligand-dependent activation of the wild-type receptor. These findings show that STI 571 selectively inhibits **c-kit** tyrosine kinase activity and downstream activation of target proteins involved in cellular proliferation and survival. This compound may be useful in treating cancers associated with increased **c-kit** kinase activity.
CT . . .

ME, metabolism
*Antineoplastic Agents: PD, pharmacology
Enzyme Activation: DE, drug effects
*Piperazines: PD, pharmacology
Protein-Tyrosine Kinase: AI, antagonists & inhibitors
***Proto-Oncogene Protein c-kit: DE, drug effects**
***Proto-Oncogene Protein c-kit: ME, metabolism**
*Pyrimidines: PD, pharmacology
*Signal Transduction: DE, drug effects
Tumor Cells, Cultured
CN 0 (Antineoplastic Agents); 0 (CGP 57148); 0 (Piperazines); 0 (Pyrimidines); EC 2.7.1.112 (Protein-Tyrosine Kinase); EC 2.7.11.- (Proto-Oncogene Protein **c-kit**)
:.

L3 ANSWER 12 OF 30 MEDLINE
AB The **c-kit** proto-oncogene encodes a 145 kd tyrosine kinase transmembrane receptor, which plays a key role in haemopoiesis. The **c-kit** has been classified as CD117 and is especially useful in the differential diagnosis of acute myelogenous leukemia (AML) and acute. . . in order to establish lineage involvement of the blastic population. The threshold used to assign positivity for CD117 was 10%. **Bcr/abl**, TEL/AML-1 and MLL rearrangements were assessed by molecular methods. CD117 expression was detected in 91% of AML and MDS. All. . . 0.44 for CD33 ($P < 0.005$). CD117 was also positive in four cases of ALL. None of these cases showed **bcr/abl** or MLL rearrangements. In the light of these findings, CD117 expression should yield a higher score, at least one point,. . .
CT . . .
PA, pathology
*Leukemia, Myeloid: IM, immunology
Leukemia, Myeloid: PA, pathology
Middle Age
*Myelodysplastic Syndromes: IM, immunology
Myelodysplastic Syndromes: PA, pathology
***Proto-Oncogene Protein c-kit: AN, analysis**
Proto-Oncogene Protein c-kit: BI, biosynthesis
Proto-Oncogene Protein c-kit: GE, genetics
CN 0 (Antigens, CD); 0 (Antigens, Differentiation, Myelomonocytic); 0 (Biological Markers); 0 (CD33 antigen); EC 2.7.11.- (Proto-Oncogene Protein **c-kit**); EC 3.4.11.2 (Antigens, CD13)
:.

L3 ANSWER 13 OF 30 MEDLINE
AB . . . The binding specificity of the Gads SH2 domain is similar to Grb2 and mediates the interaction of Gads with Shc, **Bcr-Abl** and **c-kit**. Gads does not interact with Sos, Cbl or Sam68, although the isolated carboxy terminal Gads SH3 domain is able to. . . regulates its interaction with downstream SH3 domain-binding proteins and that Gads may function to couple tyrosine-phosphorylated proteins such as Shc, **Bcr-Abl** and activated receptor tyrosine kinases to downstream effectors distinct from Sos and Ras.
CT . . . Support, Non-U.S. Gov't
3T3 Cells
Amino Acid Sequence
COS Cells
Carrier Proteins: GE, genetics
*Carrier Proteins: ME, metabolism

Cloning, Molecular
Fusion Proteins, bcr-abl: ME, metabolism
Gene Expression
K562 Cells
Mice
Molecular Sequence Data
Phosphorylation
*Proteins: ME, metabolism
Proto-Oncogene Protein c-kit: ME, metabolism
Rabbits
*Tyrosine: ME, metabolism
*src Homology Domains
CN 0 (Carrier Proteins); 0 (Fusion Proteins, **bcr-abl**); 0 (GADS protein); 0 (Proteins); 0 (Shc protein); EC 2.7.11.- (Proto-Oncogene Protein **c-kit**)
:.

L3 ANSWER 14 OF 30 MEDLINE
AB The interaction between p145(**c-KIT**) and p210(**bcr-abl**) in transduced cell lines, and the selective outgrowth of normal progenitors during long-term culture of chronic myeloid leukemia (CML) cells. . . of colony-forming unit-granulocyte-macrophage (CFU-GM) from CML CD34(+)CD38(+) cells and the more primitive CML CD34(+)CD38(-) cells. These CFU-GM colonies were all **bcr-abl** positive, showing the specificity of SCF stimulation for the leukemic cell population. Coculture of CML and normal CD34(+) cells showed. . .
CT . . .
Antigens, CD34
Bone Marrow: PA, pathology
Cell Adhesion: DE, drug effects
Cell Division: DE, drug effects
Culture Media, Serum-Free
Fibronectins
Fusion Proteins, bcr-abl: AN, analysis
Fusion Proteins, bcr-abl: PH, physiology
Hematopoietic Cell Growth Factors: SE, secretion
Hematopoietic Stem Cells: CY, cytology
Hematopoietic Stem Cells: DE,. . . Hematopoietic Stem Cells: ME, metabolism
*Leukemia, Myeloid, Philadelphia-Positive: PA, pathology
Neoplasm Proteins: AN, analysis
Neoplasm Proteins: PH, physiology
Philadelphia Chromosome
Proto-Oncogene Protein c-kit: BI, biosynthesis
Proto-Oncogene Protein c-kit: GE, genetics
*Stem Cell Factor: PD, pharmacology
Tumor Cells, Cultured: DE, drug effects
Tumor Stem Cell Assay
. . .
CN 0 (Antigens, CD34); 0 (Culture Media, Serum-Free); 0 (Fibronectins); 0 (Fusion Proteins, **bcr-abl**); 0 (Hematopoietic Cell Growth Factors); 0 (Neoplasm Proteins); 0 (Stem Cell Factor); EC 2.7.11.- (Proto-Oncogene Protein **c-kit**)
:.

L3 ANSWER 15 OF 30 MEDLINE
TI JURL-MK1 (**c-kit**(high)/CD30-/CD40-) and JURL-MK2 (**c-kit**(low)/CD30+/CD40+) cell lines: 'two-sided' model for investigating leukemic megakaryocytopoiesis.

AB . . . is hypodiploid whereas JURL-MK2 is near triploid and that both cell lines retain t(9;22). Moreover, JURL-MK1 and JURL-MK2 have a **bcr/abl**-fused gene with the same junction found in the patient's fresh cells, and both cell lines express the b3/a2 type of hybrid **bcr/abl** mRNA. The morphology and immunophenotype of these cell lines are reminiscent of megakaryoblasts. In both lines, a limited but consistent. . .

CT . . .
Surface: AN, analysis
Cell Differentiation: DE, drug effects
Cells, Cultured
Chromosome Banding
DNA, Viral: AN, analysis
Dimethyl Sulfoxide: PD, pharmacology
Fusion Proteins, bcr-abl: GE, genetics
*Hematopoiesis
Herpesvirus 4, Human: GE, genetics
Immunophenotyping
In Situ Hybridization
Karyotyping
*Leukemia, Myeloid, Philadelphia-Positive: PA, pathology
*Megakaryocytes
Middle Age
Proto-Oncogene Protein c-kit: AN, analysis
Tetradecanoylphorbol Acetate: PD, pharmacology
Translocation (Genetics)

CN 0 (Antigens, CD30); 0 (Antigens, CD40); 0 (Antigens, Surface); 0 (DNA, Viral); 0 (Fusion Proteins, **bcr-abl**); EC 2.7.11.- (Proto-Oncogene Protein **c-kit**)
:.

L3 ANSWER 16 OF 30 MEDLINE

AB The 9;22 chromosomal translocation characteristic of CML results in a fused **bcr/abl** gene and an abnormal fusion protein, p210bcr/abl. Relative to normal c-abl, p210bc1/abl has elevated tyrosine kinase activity that is essential. . . cytokines, we found a striking similarity in the tyrosine phosphorylation of four major and three minor proteins after stimulation with **c-kit** ligand (KL) and the P-tyr proteins that are constitutively phosphorylated in primary primitive lin- chronic phase CML blasts. Other cytokines tested (ie GM-CSF, G-CSF, IL-3, FLT3 ligand, TPO, EPO) were much less active or stimulated phosphorylation of other proteins. KL/**c-kit** and **bcr/abl** have some similar activities including enhancing survival and expansion of hematopoietic progenitor cells, probably acting primarily on early progenitors at. . . stem cells and primitive progenitors are at a particularly susceptible stage of development that renders them especially responsive to sustained **bcr/abl**-induced phorphorylation of a number of signaling proteins that are components of critical regulatory pathways, including **c-kit**. The affected pathways control and coordinate multiple diverse cell processes including proliferation, differentiation, maturation and apoptosis, processes that are normally. . .

CT . . . Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Adolescence
Adult
Apoptosis
Bone Marrow: PA, pathology
Cell Division
Cell Separation
Cell Survival
***Fusion Proteins, bcr-abl: PH, physiology**
Hematopoiesis

Leukemia, Myeloid, Philadelphia-Positive: GE, genetics
*Leukemia, Myeloid, Philadelphia-Positive: PA, pathology
Phosphoproteins: ME, metabolism
Phosphotyrosine: ME,. . .
CN 0 (Fusion Proteins, **bcr-abl**); 0 (Phosphoproteins); 0 (Stem Cell Factor)
:.

L3 ANSWER 17 OF 30 MEDLINE
AB Characteristic of chronic myelogenous leukemia (CML) is the presence of the chimeric p210(**bcr-abl**) protein possessing elevated protein tyrosine kinase activity relative to normal c-abl tyrosine kinase.
Hematopoietic progenitors isolated from CML patients in. . . SDS-PAGE and associates with the p120 ras GTPase-activating protein (GAP). We have purified p62(dok) from a hematopoietic cell line expressing p210(**bcr-abl**). p62(dok) is a novel protein with features of a signaling molecule. Association of p62(dok) with GAP correlates with its tyrosine phosphorylation. p62(dok) is rapidly tyrosine-phosphorylated upon activation of the **c-Kit** receptor, implicating it as a component of a signal transduction pathway downstream of receptor tyrosine kinases.
CT Check Tags: Human; Support, U.S. Gov't, P.H.S.
Cloning, Molecular
Electrophoresis, Polyacrylamide Gel
Fusion Proteins, bcr-abl: ME, metabolism
GTPase-Activating Proteins
*Hematopoietic Stem Cells: ME, metabolism
*Leukemia, Myeloid, Chronic: ME, metabolism
Phosphoproteins: CH, chemistry
Phosphoproteins: IP, isolation & purification
*Phosphoproteins: ME, metabolism
Phosphorylation
Phosphotyrosine: ME, metabolism
Protein-Tyrosine Kinase: ME, metabolism
*Proteins: ME, metabolism
Proto-Oncogene Protein c-kit: ME, metabolism
Signal Transduction
Stem Cell Factor: ME, metabolism
Tumor Cells, Cultured
ras GTPase-Activating Proteins
src Homology. . .
CN 0 (Fusion Proteins, **bcr-abl**); 0 (GTPase-Activating Proteins); 0 (Phosphoproteins); 0 (Proteins); 0 (Stem Cell Factor); 0 (p62(dok) protein); 0 (ras GTPase-Activating Proteins); EC 2.7.1.- (protein-tyrosine kinase c-src); EC 2.7.1.112 (Protein-Tyrosine Kinase); EC 2.7.11.- (Proto-Oncogene Protein **c-kit**)
:.

L3 ANSWER 18 OF 30 MEDLINE
AB The chimaeric **bcr/abl** oncogene is detected in virtually all cases of chronic myelogenous leukaemia (CML). It encodes a constitutively active tyrosine kinase of 210 kDalton, p210bcr/abl, which stimulates a variety of cytosolic signalling intermediates. The effects of **bcr/abl** on the activity of growth factor receptors are less well known. In order to investigate interaction of p210bcr/abl with the receptor tyrosine kinase p145c-kit, we used two myeloid, factor-dependent cell lines, MO7 and 32D, to generate **bcr/abl** positive sublines, MO7p210 and 32Dp210, by transfection with

the **bcr/abl** gene. Since 32D and 32Dp210 cells did not express p145c-kit, a **c-kit** retrovirus was used to generate **c-kit** positive cell lines (32Dkit, 32Dp210kit). In contrast to MO7 and 32Dkit cells, MO7p210 and 32Dp210kit cells were factor independent and. . . not affect the growth of MO7p210 cells, thus eliminating the possibility of an autocrine SF secretion. 32Dkit cells transfected with **bcr/abl** containing an inactivating point mutation (Lys-->Arg271) in the Abl kinase domain (32Dp210(Arg271)kit) retained their responsiveness to the effects of rhSF.. . . Co-immunoprecipitation experiments with anti-Kit and anti-Abl MAbs demonstrated that p145c-kit and p210bcr/abl were associated in an intracellular complex in human **bcr/abl** positive, **c-kit** positive cell lines (MO7p210; GM/SO). Finally, colony assays with bone marrow from **bcr/abl** positive CML patients showed that the haemopoietic progenitors of three of four patients did not respond to rhSF. Taken together,. . .

CT Check Tags: Human; Support, Non-U.S. Gov't
Cell Division: DE, drug effects
***Fusion Proteins, bcr-abl: ME, metabolism**
Hematopoietic Stem Cells: DE, drug effects
Hematopoietic Stem Cells: EN, enzymology
*Leukemia, Myeloid, Chronic: EN, enzymology
Leukemia, Myeloid, Chronic: GE, genetics
Precipitin Tests
Protein-Tyrosine Kinase: GE, genetics
Protein-Tyrosine Kinase: PD, pharmacology
***Proto-Oncogene Protein c-kit: ME, metabolism**
Recombinant Proteins: PD, pharmacology
*Stem Cell Factor: PD, pharmacology
Transfection
Tumor Cells, Cultured

CN 0 (Fusion Proteins, **bcr-abl**); 0 (Recombinant Proteins); 0 (Stem Cell Factor); EC 2.7.1.112 (Protein-Tyrosine Kinase); EC 2.7.11.- (Proto-Oncogene Protein **c-kit**)

:.

L3 ANSWER 19 OF 30 MEDLINE

AB . . . identity, with highest homology in the N-terminal SH3 domain. The GrapSH2 domain interacts with ligand-activated receptors for stem cell factor (**c-kit**) and erythropoietin (EpoR). Grap also forms a stable complex with the **Bcr-Abl** oncoprotein via its SH2 domain in K562 cells. Furthermore, Grap is associated with a Ras guanine nucleotide exchange factor mSos1,. . .

:.

L3 ANSWER 20 OF 30 MEDLINE

TI **c-kit** ligand stimulates tyrosine phosphorylation of a similar pattern of phosphotyrosyl proteins in primary primitive normal hematopoietic progenitors that are constitutively. . .

AB Characteristic of Philadelphia (Ph)+ chronic myelogenous leukemia (CML) is the presence of the chimeric **BCR/ABL** (p210) protein possessing elevated protein tyrosine kinase activity relative to the normal c-abl tyrosine kinase. Our previous studies demonstrated subtle.

. 140, 110, 62 and 56 kDa) and three minor (approximately 51, 45 and 42 kDa) P-tyr proteins after stimulation with **c-kit** ligand and the P-tyr proteins constitutively phosphorylated in primary primitive lin- chronic phase CML blasts. Other growth factors tested (ie. . . phosphorylation of other proteins. It is provocative that at least

seven proteins rapidly and transiently phosphorylated on tyrosine in the **c-kit** ligand signal transduction pathway in lin- normal blasts may be constitutive substrates for the p210 activated tyrosine kinase in comparable. . . phase CML blasts. In addition, it is intriguing that some of the biological effects on hematopoietic progenitors attributed to the **c-kit** ligand may be similar to some of the observed biological consequences of the p210 protein, including survival and expansion of. . .

CT Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Cell Lineage
Electrophoresis, Polyacrylamide Gel
Fusion Proteins, bcr-abl: ME, metabolism
GTPase-Activating Proteins
Hematopoietic Cell Growth Factors: PD, pharmacology
*Hematopoietic Stem Cells: ME, metabolism
Hematopoietic Stem. . .

CN 0 (Fusion Proteins, **bcr-abl**); 0 (GTPase-Activating Proteins); 0 (Hematopoietic Cell Growth Factors); 0 (Proteins); 0 (Stem Cell Factor); 0 (ras GTPase-Activating Proteins)

:.

L3 ANSWER 21 OF 30 MEDLINE

AB Long-term culture of marrow from patients with chronic myelogenous leukemia (CML) has been reported to favor the outgrowth of **bcr/abl**- progenitor cells in some patients. We examined the effect of the presence of soluble or transmembrane forms of stem cell. . . 3 weeks, but by 5 weeks was similar to the clonagenic cell output from the other culture conditions. Analysis of **bcr/abl** transcripts from individual colonies showed a lower percentage of malignant progenitors present in long-term cultures completely deficient in SCF than. . .

CT Check Tags: Human
Adult
Base Sequence
*Bone Marrow: PA, pathology
Cell Division
Connective Tissue: PH, physiology
Fusion Proteins, bcr-abl: AN, analysis
Gene Expression Regulation, Leukemic
*Hematopoiesis
Hematopoietic Cell Growth Factors: DF, deficiency
*Hematopoietic Cell Growth Factors:. . . *Hematopoietic Stem Cells: PA, pathology
*Leukemia, Myeloid, Philadelphia-Positive: PA, pathology
Molecular Sequence Data
*Neoplasm Proteins: PH, physiology
Polymerase Chain Reaction
Proto-Oncogene Protein c-kit
Proto-Oncogene Proteins: PH, physiology
Receptor Protein-Tyrosine Kinases: PH, physiology
Receptors, Colony-Stimulating Factor: PH, physiology
Selection (Genetics)
Stem. . .

CN 0 (Fusion Proteins, **bcr-abl**); 0 (Hematopoietic Cell Growth Factors); 0 (Neoplasm Proteins); 0 (Proto-Oncogene Proteins); 0 (Receptors, Colony-Stimulating Factor); 0 (Stem Cell Factor); EC 2.7.11.- (Proto-Oncogene Protein **c-kit**); EC 2.7.11.- (Receptor Protein-Tyrosine Kinases)

:.

L3 ANSWER 22 OF 30 MEDLINE

AB . . . ranging from 7.2 to 7.8), does not appear to be immunologically related to the beta subunit of the interleukin-3 receptor, **c-Kit**, **BCR**, **ABL**, JAK1, JAK2, Sos1, eps15, or insulin receptor substrate 1 protein. Silver-stained sodium dodecyl sulfate gels indicate that the association of. . .

:.

L3 ANSWER 23 OF 30 MEDLINE

GEN B0myb; BCr; K-ras; N-myc; N-ras; **bcr-abl**; blk; c-Ha-ras; c-abl; c-erbA; c-fes; c-fms; c-fos; c-jun; c-kit; c-myb; c-myc; c-raf-1; c-src; cdc2; lck; mos

:.

L3 ANSWER 24 OF 30 MEDLINE

AB . . . pathways are sensitive to inhibition by Tyrphostins with, nonetheless, a quantitative difference. All Tyrphostins tested are more potent inhibitors of **c-Kit** than of GM-CSF receptor triggered pathways, the most striking being Tyrphostin B42 that is 10 times more potent. In contrast. . . 2',7'-bis(2-carboxyethyl)-5-carboxyfluorescein. Taken together, our data indicate that input from two distinct pathways with discrepancy in immediate early events, that of **c-Kit** and GM-CSF receptor, results in a common output, activation of the Na+/H+ antiporter and suppression of apoptosis by the two. . .

CT . . .

Cell Division: DE, drug effects
Cell Line
Cell Survival: DE, drug effects
DNA: BI, biosynthesis
*DNA: ME, metabolism
DNA Damage
Fusion Proteins, bcr-abl: BI, biosynthesis
*Granulocyte-Macrophage Colony-Stimulating Factor: PD, pharmacology
*Hematopoietic Cell Growth Factors: PD, pharmacology
*Hematopoietic Stem Cells: CY,. . .

CN 0 (Alkaloids); 0 (Catechols); 0 (Fusion Proteins, **bcr-abl**); 0 (Hematopoietic Cell Growth Factors); 0 (Interleukin-3); 0 (Nitriles); 0 (Recombinant Proteins); 0 (Stem Cell Factor); EC 2.7.1.37 (Protein Kinases)

:.

L3 ANSWER 25 OF 30 MEDLINE

AB . . . vivo as well. Herein I review the experience of my laboratory in using this approach to target the c-myb and **c-kit** proto-oncogenes in human leukemic cells. Our results suggest that use of oligodeoxynucleotides for disrupting the function of specific genes may. . .

CT Check Tags: Animal; Human; Support, U.S. Gov't, P.H.S.
Base Sequence
Cell Line
Clone Cells: DE, drug effects
Fusion Proteins, bcr-abl: PD, pharmacology
Hematopoietic Stem Cells: DE, drug effects
Leukemia, Erythroblastic, Acute: DT, drug therapy
Leukemia, Erythroblastic, Acute:. . . Chronic: DT, drug therapy
Leukemia, Myeloid, Chronic: PA, pathology
Mice
Molecular Sequence Data
Oligodeoxyribonucleotides: GE, genetics
*Oligodeoxyribonucleotides: TU, therapeutic use
Proto-Oncogene Protein c-kit

Proto-Oncogene Proteins: PD, pharmacology
Proto-Oncogene Proteins c-myb
Receptor Protein-Tyrosine Kinases: PD, pharmacology
Receptors, Colony-Stimulating Factor
Tumor Stem. . .
CN 0 (Fusion Proteins, **bcr-abl**); 0
(Oligodeoxyribonucleotides); 0 (Proto-Oncogene Proteins); 0
(Proto-Oncogene Proteins c-myb); 0 (Receptors, Colony-Stimulating
Factor);
EC 2.7.11.- (Proto-Oncogene Protein **c-kit**); EC
2.7.11.- (Receptor Protein-Tyrosine Kinases)
GEN **bcr/abl**
:.

L3 ANSWER 26 OF 30 MEDLINE
AB . . . cell lines transfected with a p210bcr-abl expression vector.
There appeared to be a higher order complex containing Shc, Grb2, and
bcr-abl proteins. In contrast to p210bcr-abl transformed
cells, in which there was constitutive tight association between Grb2 and
Shc, binding between. . . cell line. The SLF-dependent association
between Grb2 and Shc in nontransformed cells involved formation of a
complex of Grb2 with **c-kit** receptor after SLF
treatment. Thus, p210bcr-abl appears to function in a hematopoietic
p21ras
activation pathway to allow growth factor-independent coupling. . .
which exists in a complex with the guanine nucleotide exchange factor
(Sos), and p21ras. Shc may not be required for Grb2-**c-**
kit interaction, because it fails to bind strongly to **c-**
kit.
CT . . . Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.;
Support, U.S. Gov't, P.H.S.
Bone Marrow: CY, cytology
Cell Line, Transformed
Cells, Cultured
***Fusion Proteins, bcr-abl: ME, metabolism**
Hematopoietic Cell Growth Factors: ME, metabolism
*Hematopoietic Stem Cells: ME, metabolism
Mice
*Oncogene Protein p21(ras): ME, metabolism
Phosphorylation
Precipitin Tests
*Proteins: ME, metabolism
Proto-Oncogene Protein c-kit
*Proto-Oncogene Proteins: ME, metabolism
*Receptor Protein-Tyrosine Kinases: ME, metabolism
*Receptor, Epidermal Growth Factor: ME, metabolism
*Receptors, Colony-Stimulating. . .
CN 0 (46-kDa Shc protein); 0 (52-kDa Shc protein); 0 (Fusion Proteins,
bcr-abl); 0 (Hematopoietic Cell Growth Factors); 0
(Proteins); 0 (Proto-Oncogene Proteins); 0 (Receptors, Colony-Stimulating
Factor); 0 (Stem Cell Factor); 0 (growth factor receptor-bound
protein-2);
EC 2.7.11.- (Proto-Oncogene Protein **c-kit**); EC
2.7.11.- (Receptor Protein-Tyrosine Kinases); EC 2.7.11.- (Receptor,
Epidermal Growth Factor); EC 3.6.1.- (Oncogene Protein p21(ras))
GEN **bcr-abl**; ras
:.

L3 ANSWER 27 OF 30 MEDLINE
AB . . . AS ODN inhibited growth of CML CFU-GM in a dose dependent,
sequence specific manner in approximately 75% of cases evaluated.
Bcr-abl expression was either greatly decreased or

nondetectable in the residual colonies and no residual leukemic CFU were demonstrable upon re-plating of treated cells. AS ODN that target the **c-kit** protooncogene also inhibit CML CFU and lead to downregulation of **bcr-abl** in responding cells in approximately 50% of cases. Therefore, AS ODN may prove to be useful purging agents. Most recently, we have treated SCID mice engrafted with **bcr-abl** expressing human K562 cell leukemia with phosphorothioate modified AS ODN. We have found that treated mice survive three to eight. . .

CT . . . Animal; Female; Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Base Sequence
Blast Crisis: PA, pathology
Drug Screening Assays, Antitumor
Fusion Proteins, bcr-abl: GE, genetics
Leukemia, Erythroblastic, Acute: PA, pathology
Leukemia, Erythroblastic, Acute: TH, therapy
Leukemia, Myeloid, Chronic: PA, pathology
. . . Proteins: AI, antagonists & inhibitors
Neoplasm Proteins: GE, genetics
Neoplasm Transplantation
Oligonucleotides, Antisense: PD, pharmacology
*Oligonucleotides, Antisense: TU, therapeutic use
Proto-Oncogene Protein c-kit
*Proto-Oncogene Proteins: AI, antagonists & inhibitors
Proto-Oncogene Proteins: GE, genetics
Proto-Oncogene Proteins c-myb
*Receptor Protein-Tyrosine Kinases: AI,. . .

CN 0 (Fusion Proteins, **bcr-abl**); 0 (Neoplasm Proteins); 0 (Oligonucleotides, Antisense); 0 (Proto-Oncogene Proteins); 0 (Proto-Oncogene Proteins c-myb); 0 (Receptors, Colony-Stimulating Factor);
0 (Thionucleotides); EC 2.7.11.- (Proto-Oncogene Protein **c-kit**); EC 2.7.11.- (Receptor Protein-Tyrosine Kinases)

GEN **bcr-abl**; c-abl; c-kit; c-myb

:.

L3 ANSWER 28 OF 30 MEDLINE

CT Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Bone Marrow: CY, cytology
Cells, Cultured
Fusion Proteins, bcr-abl: GE, genetics
Hematopoiesis: GE, genetics
Hematopoietic Stem Cells: CY, cytology
*Leukemia: DT, drug therapy
Leukocytes, Mononuclear: CY, cytology
*Oligodeoxyribonucleotides: TU, therapeutic use
*Oligonucleotides, Antisense: TU, therapeutic use
*Oncogenes: DE, drug effects
Proto-Oncogene Protein c-kit
Proto-Oncogene Proteins: GE, genetics
Receptor Protein-Tyrosine Kinases: GE, genetics
Receptors, Colony-Stimulating Factor: GE, genetics

CN 0 (Fusion Proteins, **bcr-abl**); 0 (Oligodeoxyribonucleotides); 0 (Oligonucleotides, Antisense); 0 (Proto-Oncogene Proteins); 0 (Receptors, Colony-Stimulating Factor); EC 2.7.11.- (Proto-Oncogene Protein **c-kit**); EC 2.7.11.- (Receptor Protein-Tyrosine Kinases)

:.

L3 ANSWER 29 OF 30 MEDLINE

AB . . . K562 cells express the c-myb protooncogene, which served as the

target for the antisense DNA. They also express the tumor-specific **bcr-abl** oncogene that was utilized to track the human cells in the mouse host. Once circulating leukemic blast cells had been.
. .

CT Check Tags: Animal; Female; Human; Support, U.S. Gov't, P.H.S.
Base Sequence
Fusion Proteins, bcr-abl: GE, genetics
Gene Expression
*Leukemia: TH, therapy
Mice
Mice, SCID
Molecular Sequence Data
Neoplasm Transplantation
Oligonucleotides, Antisense: CH, chemistry
*Oligonucleotides, Antisense: TU, therapeutic use
*Oncogenes
Proto-Oncogene Protein c-kit
*Proto-Oncogene Proteins: GE, genetics
Proto-Oncogene Proteins c-myb
RNA, Messenger
Survival Analysis
Tumor Cells, Cultured

CN 0 (Fusion Proteins, **bcr-abl**); 0 (Oligonucleotides, Antisense); 0 (Proto-Oncogene Proteins); 0 (Proto-Oncogene Proteins c-myb); 0 (RNA, Messenger); EC 2.7.11.- (Proto-Oncogene Protein **c-kit**)

GEN **bcr-abl**; c-kit; c-myb

:.

L3 ANSWER 30 OF 30 MEDLINE

GEN bcr; **bcr-abl**; c-abl; c-kit; c-myc; c-onc; myl

:end

SUMMARY

=> D HIS

(FILE 'HOME' ENTERED AT 14:59:15 ON 18 AUG 2000)

FILE 'REGISTRY' ENTERED AT 14:59:20 ON 18 AUG 2000
L1 STR
L2 0 S L1
L3 STR L1
L4 1 S L3
L5 STR L3
L6 39 S L5 FUL

FILE 'CAPLUS' ENTERED AT 15:01:55 ON 18 AUG 2000
L7 31 S L6

FILE 'REGISTRY' ENTERED AT 15:02:04 ON 18 AUG 2000
L8 STR L1
L9 STR
L10 0 S L9 SSS SAM SUB=L6
L11 3 S L9 SSS FUL SUB=L6 ← 3 compounds Reg.

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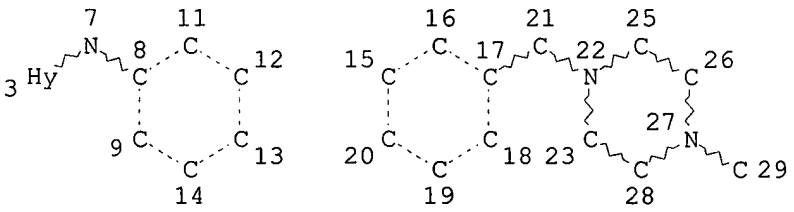
L12 21 S L11 ← 21 cites caplus

FILE 'CAOLD' ENTERED AT 15:08:34 ON 18 AUG 2000
L13 0 S L11 — Ø cites caold

FILE 'BEILSTEIN' ENTERED AT 15:08:42 ON 18 AUG 2000
L14 QUE L9
L15 2 S L1 AND L9 FUL
L16 0 S L11
L17 2 S L15 AND PRE/FA ← 2 compounds Beilstein

=> D QUE L11

L5 STR



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DEFAULT ECLEVEL IS LIMITED
ECOUNT IS E4 C E2 N AT 3

GRAPH ATTRIBUTES:
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NUMBER OF NODES IS 22

STEREO ATTRIBUTES: NONE
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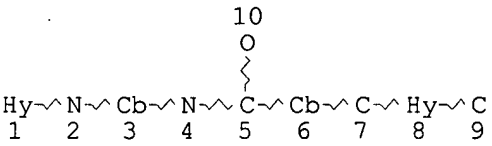

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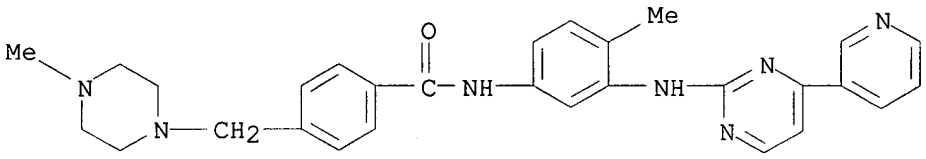
DEFAULT ECLEVEL IS LIMITED
ECOUNT IS E4 C E2 N AT 1
ECOUNT IS E4 C E2 N AT 8

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 10

STEREO ATTRIBUTES: NONE
L11 3 SEA FILE=REGISTRY SUB=L6 SSS FUL L9

=> D BIB ABS HITSTR

L12 ANSWER 1 OF 21 CAPLUS COPYRIGHT 2000 ACS
AN 2000:531938 CAPLUS
TI Leukemia therapy with tyrosine kinase inhibitor
AU Tojyo, Arinobu
CS Dep. Hematol./Oncol., The Inst. Med. Sci., The Univ. Tokyo, Japan
SO Saishin Igaku (2000), 55(8), 1851-1855
CODEN: SAIGAK; ISSN: 0370-8241
PB Saishin Igakusha
DT Journal; General Review
LA Japanese
AB A review with 6 refs., on tyrosine kinases expressed in the blood cells, induction of leukemia by Bcr-Abl kinase, therapeutic strategy for chronic myelogenous leukemia targeting Bcr-Abl kinase, and development of Bcr-Abl kinase inhibitor CGP 57148 (STI 571).
IT **152459-95-5**, CGP 57148
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); BIOL (Biological study)
(leukemia therapy with tyrosine kinase inhibitor)
RN 152459-95-5 CAPLUS
CN Benzamide, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]- (9CI) (CA INDEX NAME)



=> D BIB ABS HITSTR 2

L12 ANSWER 2 OF 21 CAPLUS COPYRIGHT 2000 ACS
AN 2000:493544 CAPLUS
TI High affinity enzyme inhibitors and therapeutic uses thereof
IN Shokat, Kevan M.
PA Princeton University, USA
SO PCT Int. Appl., 169 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000042042	A2	20000720	WO 2000-US551	20000111

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

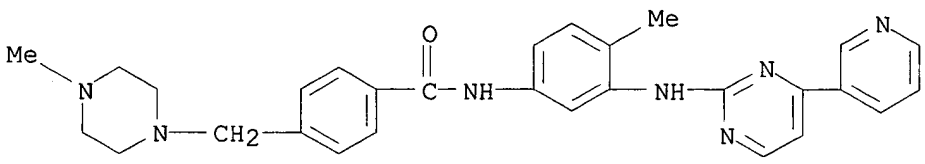
PRAI US 1999-115340 19990111
US 1999-145422 19990723

AB The invention provides general methods for discovering mutant inhibitors for any class of enzymes as well as the specific inhibitors so identified.

More specifically, the invention provides general methods for discovering specific inhibitors for multi-substrate enzymes. Examples of such multi-substrate enzymes include, but are not limited to, kinases and transferases. The mutant inhibitors identified by the methods of the invention can be used to highly selectively disrupt cell functions such as

oncogenic transformation. In one particular example, the invention provides an Src protein kinase inhibitor, pharmaceutical compns. thereof and methods of disrupting transformation in a cell that expresses the target v-src comprising contacting the cell with the protein kinase inhibitor.

IT **152459-95-5**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(high affinity enzyme inhibitors and therapeutic uses)
RN 152459-95-5 CAPLUS
CN Benzamide, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]- (9CI) (CA INDEX NAME)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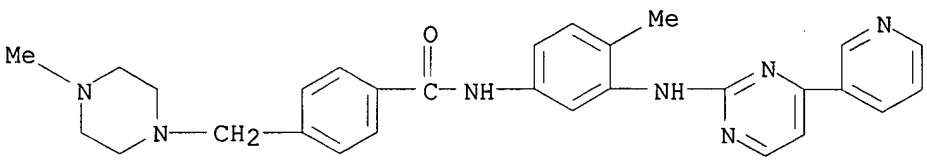
=> D BIB ABS HITSTR 3

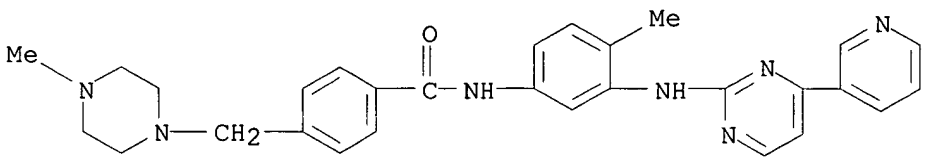
L12 ANSWER 3 OF 21 CAPLUS COPYRIGHT 2000 ACS
AN 2000:379129 CAPLUS
TI Mechanism of resistance to the ABL tyrosine kinase inhibitor STI571 in BCR/ABL-transformed hematopoietic cell lines
AU Weisberg, Ellen; Griffin, James D.
CS Department of Adult Oncology, Dana Farber Cancer Institute, Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA
SO Blood (2000), 95(11), 3498-3505
CODEN: BLOOAW; ISSN: 0006-4971
PB American Society of Hematology
DT Journal
LA English
AB The tyrosine kinase activity of the Bcr/Abl oncogene is required for transformation of hematopoietic cells. The tyrosine kinase inhibitor STI571 (formerly called CGP57148B, Novartis Pharmaceuticals) inhibits BCR/ABL, TEL/ABL, and v-ABL kinase activity and inhibits growth and viability of cells transformed by any of these ABL oncogenes. Here we report the generation of 2 BCR/ABL-pos. cell lines that have developed partial resistance to STI571. BCR/ABL-transformed Ba/F3 hematopoietic cells and Philadelphia-pos. human K562 cells were cultured in gradually increasing concns. of STI571 over a period of several months to generate resistant lines. Resistant Ba/F3.p210 cells were found to have an increase in Bcr/Abl mRNA, amplification of the Bcr/Abl transgene, and a greater than tenfold increase in the level of BCR/ABL protein. In contrast to Ba/F3.p210 cells, drug-resistant K562 cells did not undergo detectable amplification of the BCR/ABL gene, although they displayed a 2-fold to 3-fold increase in p210BCR/ABL protein. The addn. of STI571 to both resistant Ba/F3.p210 and K562 cells resulted in a rapid redn. of tyrosine phosphorylation of cellular proteins, similar to that obsd. for nonresistant cells. However, the inhibition of kinase activity was transient and partial and was not accompanied by apoptosis. The results suggest that resistance to STI571 may be multifactorial. Increased expression of the target protein BCR/ABL was obsd. in both lines, and resulted from oncogene amplification in one line. However, altered drug metab., transport, or other related mechanisms may also contribute to drug resistance.
IT **152459-95-5**, STI 571
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(resistance to TK inhibitor STI571 in BCR/ABL and Ba/F3 hematopoietic cells)
RN 152459-95-5 CAPLUS
CN Benzamide, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]- (9CI) (CA INDEX NAME)



RE.CNT 36
RE
(1) Anafi, M; Blood 1993, V82, P3524 CAPLUS
(2) Ben-Neriah, Y; Science 1986, V233, P212 CAPLUS
(3) Beran, M; Clin Cancer Res 1998, V4, P1661 CAPLUS
(4) Bostock, C; Cell 1980, V19, P709 CAPLUS
(5) Buchdunger, E; Cancer Res 1996, V56, P100 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> D BIB ABS HITSTR 4

L12 ANSWER 4 OF 21 CAPLUS COPYRIGHT 2000 ACS
AN 2000:145381 CAPLUS
DN 132:303099
TI Induction of resistance to the Abelson inhibitor STI571 in human leukemic cells through gene amplification
AU Le Coutre, Philipp; Tassi, Elena; Varella-Garcia, Marileila; Barni, Rossella; Mologni, Luca; Cabrita, Goncalo; Marchesi, Edoardo; Supino, Rosanna; Gambacorti-Passerini, Carlo
CS Department of Experimental Oncology, Istituto Nazionale Tumori, Milan, 20133, Italy
SO Blood (2000), 95(5), 1758-1766
CODEN: BLOOAW; ISSN: 0006-4971
PB American Society of Hematology
DT Journal
LA English
AB The 2-phenylaminopyrimidine deriv. STI571 has been shown to selectively inhibit the tyrosine kinase domain of the oncogenic bcr/abl fusion protein. The activity of this inhibitor has been demonstrated so far both in vitro with bcr/abl expressing cells derived from leukemic patients, and in vivo on nude mice inoculated with bcr/abl pos. cells. Yet, no information is available on whether leukemic cells can develop resistance to bcr/abl inhibition. The human bcr/abl expressing cell line LAMA84 was cultured with increasing concns. of STI571. After approx. 6 mo of culture, a new cell line was obtained and named LAMA84R. This newly selected cell line showed an IC50 for the STI571 (1.0 .mu.M) 10-fold higher than the IC50 (0.1 .mu.M) of the parental sensitive cell line. Treatment with STI571 was shown to increase both the early and late apoptotic fraction in LAMA84 but not in LAMA84R. The induction of apoptosis in LAMA84 was assocd. with the activation of caspase 3-like activity, which did not develop in the resistant LAMA84R cell line. LAMA84R cells showed increased levels of bcr/abl protein and mRNA when compared to LAMA84 cells. FISH anal. with BCR- and ABL-specific probes in LAMA84R cells revealed the presence of a marker chromosome contg. approx. 13 to 14 couples of the BCR/ABL gene. Thus, overexpression of the Bcr/Abl protein mediated through gene amplification is assocd. with and probably dets. resistance of human leukemic cells to STI571 in vitro.
IT **152459-95-5**, STI 571
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(induction of resistance to the abelson inhibitor STI571 in human leukemic cells through gene amplification)
RN 152459-95-5 CAPLUS
CN Benzamide, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]- (9CI) (CA INDEX NAME)



RE.CNT 21
RE
(1) Amarante-Mendes, G; Blood 1998, V91, P1700 CAPLUS
(2) Buchdunger, E; Cancer Res 1996, V56, P100 CAPLUS
(3) Cambier, N; Oncogene 1998, V16, P335 CAPLUS
(4) Daley, G; Science 1990, V247, P824 CAPLUS
(5) Deininger, M; Blood 1997, V90, P3691 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> D BIB ABS HITSTR 5

L12 ANSWER 5 OF 21 CAPLUS COPYRIGHT 2000 ACS
AN 2000:133467 CAPLUS
DN 132:175828
TI Method using phthalazine derivatives for treating ocular neovascular diseases
IN Brazzell, Romulus Kimbro; Wood, Jeanette Marjorie; Campochiaro, Peter Anthony; Kane, Frances Elizabeth
PA Novartis A.-G., Switz.; Novartis-Erfindungen Verwaltungsgesellschaft m.b.H.
SO PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000009098	A2	20000224	WO 1999-EP5876	19990811
	WO 2000009098	A3	20000518		
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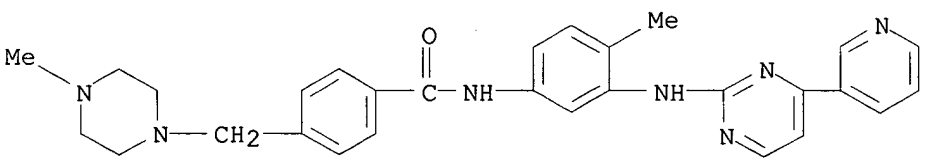
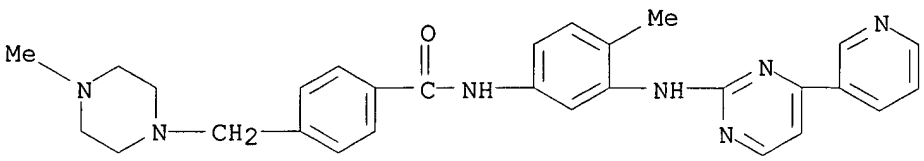
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 9957330	A1	20000306	AU 1999-57330	19990811
PRAI	US 1998-133855	19980813			
	WO 1999-EP5876	19990811			

OS MARPAT 132:175828
AB Phthalazines are used in the prepn. of medicaments for the treatment of ocular neovascularization.
IT **152459-95-5**, CGP 57148
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(phthalazine derivs. for treating ocular neovascular diseases)
RN 152459-95-5 CAPLUS
CN Benzamide, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]- (9CI) (CA INDEX NAME)



=> D BIB ABS HITSTR 6

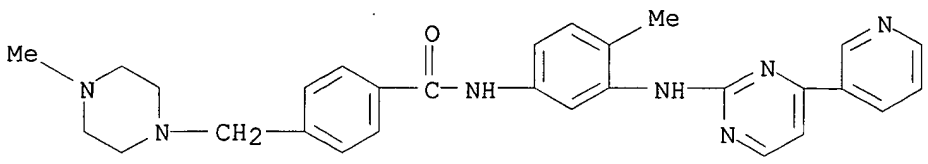
L12 ANSWER 6 OF 21 CAPLUS COPYRIGHT 2000 ACS
AN 1999:641704 CAPLUS
DN 131:281179
TI Favorable therapeutic index of a p210BCR-ABL-specific tyrosine kinase inhibitor; activity on lineage-committed and primitive chronic myelogenous leukemia progenitors
AU Kasper, Bernd; Fruehauf, Stefan; Schiedlmeier, Bernd; Buchdunger, Elisabeth; Ho, Anthony D.; Zeller, W. Jens
CS German Cancer Research Center, Heidelberg, D-69120, Germany
SO Cancer Chemother. Pharmacol. (1999), 44(5), 433-438
CODEN: CCPHDZ; ISSN: 0344-5704
PB Springer-Verlag
DT Journal
LA English
AB To study the effect of the Tyr kinase inhibitor CGP37148B on lineage-committed and primitive chronic myelogenous leukemia (CML) progenitor cells, peripheral blood progenitor cells (PBPC) mobilized in chronic phase CML were exposed to this compd. in vitro. Both short-term (.ltoreq.1 wk) and long-term exposure (.gtoreq.2 wk) to CGP57148B were investigated using suspension culture, semisolid (methylcellulose) assay or stroma-dependent long-term culture (LTC). The proportion of bcr/abl-pos. progenitors was detd. after direct plating [2 wk in colony-forming cell (CFC) assay] as well as after 2 or 6 wk LTC (LTC always followed by CFC replates). Incubation of CML PBPC over 48 h in suspension culture with 100 .mu.M CGP57148B reduced the proportion of bcr/abl-pos. colonies to 4.4% after direct plating, 6.6% after 2 wk LTC and 5% after 6 wk LTC. At this dose, survival of drug-exposed normal PBPC was 53%, 51%, and 54.5%, resp. Incubation with CGP57148B at a concn. of 10 .mu.M over 1 wk under LTC conditions reduced the no. of bcr/abl-pos. colonies to 11.8% after direct plating, 12% after 2 wk LTC and 14.3% after 6 wk LTC; survival of normal PBPC was 84.5%, 93% and 86%, resp. Following long-term exposure to CGP57148B at a concn. of 1 .mu.M, the proportion of remaining bcr/abl-pos. colonies was 35%, 9% and 25% of untreated CML samples after direct plating as well as after 2 and 6 wk LTC, resp. The resp. values for 10 .mu.M CGP57148B were 10%, 11% and 19%. Long-term exposure of normal progenitors to CGP57148B yielded a survival of 98%, 100%, and 93% (1 .mu.M) or 77%, 86%, and 80% (10 .mu.M), resp. The results support the use of CGP57148B either for short-term exposure in vitro (e.g. purging) or for continuous treatment of CML in vivo.
IT **152459-95-5**, CGP 57148B
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(CGP 57148B; CGP57148B, a p210BCR-ABL-specific tyrosine kinase inhibitor; therapeutic index and activity on lineage-committed and primitive chronic myelogenous leukemia progenitors)
RN 152459-95-5 CAPLUS
CN Benzamide, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]- (9CI) (CA INDEX NAME)



RE.CNT 27
RE
(1) Anafi, M; Blood 1993, V82, P3524 CAPLUS
(3) Buchdunger, E; Cancer Res 1996, V56, P100 CAPLUS
(4) Carroll, M; Blood 1997, V90, P4947 CAPLUS
(7) Cox, M; Am J Clin Pathol 1998, V109, P24 CAPLUS
(9) de Klein, A; Nature 1982, V300, P765 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> D BIB ABS HITSTR 7

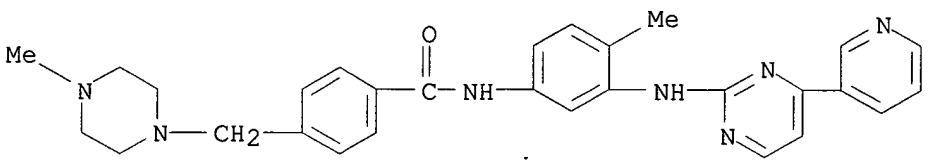
L12 ANSWER 7 OF 21 CAPLUS COPYRIGHT 2000 ACS
AN 1999:413549 CAPLUS
DN 131:223278
TI Selective tyrosine kinase inhibitor for the platelet-derived growth factor receptor in vitro inhibits smooth muscle cell proliferation after reinjury of arterial intima in vivo
AU Myllarniemi, Marjukka; Frosen, Juhana; Ramirez, Lazaro G. Calderon; Buchdunger, Elisabeth; Lemstrom, Karl; Hayry, Pekka
CS Transplantation Laboratory, University of Helsinki, Helsinki, FIN-00014, Finland
SO Cardiovasc. Drugs Ther. (1999), 13(2), 159-168
CODEN: CDTHET; ISSN: 0920-3206
PB Kluwer Academic Publishers
DT Journal
LA English
AB The long-term success of coronary angioplasty is limited by restenosis. This study was undertaken to investigate whether and to what extent the enhanced proliferative response obsd. in a balloon reinjury model of rat aorta is regulated by the PDGF receptor (PDGF-R). Balloon injury was performed to 14-day-old pre-existing neointimal lesion in rat aorta. PDGF receptor and ligand immunoreactivity were measured at several time points after the first and second injury, and PDGF-R signaling was blocked with a selective inhibitor of PDGF-R tyrosine kinase. In the neointima, after repeated injury, upregulation of PDGF-AA was seen to coincide with a prompt proliferative response of smooth muscle cells (SMC). Administration of the PDGF-R tyrosine kinase inhibitor in vivo, tested and found to inhibit the proliferation of SMC induced by PDGF-AA and PDGF-BB, but not by IGF-1, EGF, or bFGF, resulted in a 60% redn. in the abs. no. and percentage of BrdU + cells after the second balloon injury to pre-existing neointima, but had no significant effect on proliferation after the first injury. Endpoint lesion area was reduced by 50% in the treated group at 14 days after the second injury. The results suggest that systemic administration of a tyrosine kinase inhibitor specific for the PDGF-R can be useful in the prevention of restenosis.
IT **152459-95-5**, CGP 57148B
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(tyrosine kinase inhibitor for PDGF receptor inhibits smooth muscle cell proliferation after reinjury of arterial intima)
RN 152459-95-5 CAPLUS
CN Benzamide, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]- (9CI) (CA INDEX NAME)



RE.CNT 38
RE
(1) Banai, S; Circulation 1998, V97, P1960 CAPLUS
(2) Buchdunger, E; Cancer Res 1996, V56, P100 CAPLUS
(3) Buchdunger, E; Proc Natl Acad Sci USA 1995, V92, P2558 CAPLUS
(4) Calara, F; Arterioscler Thromb Vasc Biol 1996, V16, P187 CAPLUS
(7) Courtman, D; Circ Res 1998, V82, P996 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> D BIB ABS HITSTR 8

L12 ANSWER 8 OF 21 CAPLUS COPYRIGHT 2000 ACS
AN 1999:153904 CAPLUS
DN 130:323679
TI TEL/PDGF.beta.R induces hematologic malignancies in mice that respond to a specific tyrosine kinase inhibitor
AU Tomasson, Michael H.; Williams, Ifor R.; Hasserjian, Robert; Udomsakdi, Chirayu; McGrath, Shannon M.; Schwaller, Juerg; Druker, Brian; Gilliland, D. Gary
CS Division of Hematology, Brigham and Women's Hospital, Boston, MA, 02115, USA
SO Blood (1999), 93(5), 1707-1714
CODEN: BLOOAW; ISSN: 0006-4971
PB W. B. Saunders Co.
DT Journal
LA English
AB The TEL/PDGF.beta.R fusion protein is expressed as the consequence of a recurring t(5;12) translocation assocd. with chronic myelomonocytic leukemia (CMML). Unlike other activated protein tyrosine kinases assocd. with hematopoietic malignancies, TEL/PDGF.beta.R is invariably assocd. with a myeloid leukemia phenotype in humans. To test the transforming properties of TEL/PDGF.beta.R in vivo, and to analyze the basis for myeloid lineage specificity in humans, the authors constructed transgenic mice with TEL/PDGF.beta.R expression driven by a lymphoid-specific Ig enhancer-promoter cassette. These mice developed lymphoblastic lymphomas of both T and B lineage, demonstrating that TEL/PDGF.beta.R is a transforming protein in vivo, and that the transforming ability of this fusion is not inherently restricted to the myeloid lineage. Treatment of TEL/PDGF.beta.R transgenic animals with a protein tyrosine kinase inhibitor with in vitro activity against PDGF.beta.R (CGP57148) resulted in suppression of disease and a prolongation of survival. A therapeutic benefit was apparent both in animals treated before the development of overt clonal disease and in animals transplanted with clonal tumor cells. These results suggest that small-mol. tyrosine kinase inhibitors may be effective treatment for activated tyrosine kinase-mediated malignancies both early in the course of disease and after the development of addnl. transforming mutations.
IT **152459-95-5**, CGP57148
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(TEL/PDGF.beta.R fusion protein induces hematol. malignancies in mice that respond to specific tyrosine kinase inhibitor)
RN 152459-95-5 CAPLUS
CN Benzamide, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]- (9CI) (CA INDEX NAME)

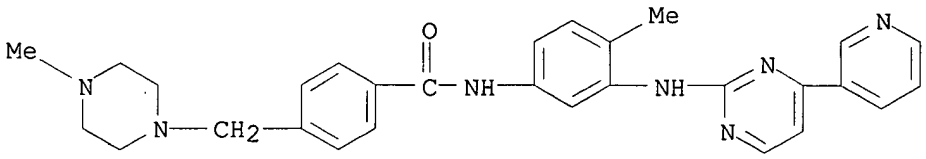


RE.CNT 32
RE
(4) Blankenstein, T; Nucleic Acids Res 1988, V16, P10939 CAPLUS
(5) Buchdunger, E; Cancer Res 1996, V56, P100 CAPLUS
(6) Buchdunger, E; Proc Natl Acad Sci USA 1995, V92, P2558 CAPLUS
(7) Buffone, G; Clin Chem 1985, V31, P164 CAPLUS
(8) Carroll, M; Blood 1997, V90, P4947 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> D BIB ABS HITSTR 9

L12 ANSWER 9 OF 21 CAPLUS COPYRIGHT 2000 ACS
AN 1999:103888 CAPLUS
DN 130:332380
TI In vivo eradication of human BCR/ABL-positive leukemia cells with an ABL kinase inhibitor
AU Le Coutre, Philipp; Mologni, Luca; Cleris, Loredana; Marchesi, Edoardo; Buchdunger, Elisabeth; Giardini, Roberto; Formelli, Franca; Gambacorti-Passerini, Carlo
CS Department of Experimental Oncology, Istituto Nazionale Tumori, Milan, 20133, Italy
SO J. Natl. Cancer Inst. (1999), 91(2), 163-168
CODEN: JNCIEQ; ISSN: 0027-8874
PB Oxford University Press
DT Journal
LA English
AB The leukemia cells of approx. 95% of patients with chronic myeloid leukemia and 30%-50% of adult patients with acute lymphoblastic leukemia express the Bcr/Abl oncoprotein, which is the product of a fusion gene created by a chromosomal translocation [(9:22) (q34;q11)]. This oncoprotein expresses a constitutive tyrosine kinase activity that is crucial for its cellular transforming activity. In this study, we evaluated the antineoplastic activity of CGP57148B, which is a competitive inhibitor of the Bcr/Abl tyrosine kinase. Nude mice were given an injection of the Bcr/Abl-pos. human leukemia cell lines KU812 or MC3. Tumor-bearing mice were treated i.p. or orally with CGP57148B according to three different schedules. In vitro drug wash-out expts. and in vivo mol. pharmacokinetic expts. were performed to optimize the in vivo treatment schedule. Treatment schedules administering CGP57148B once or twice per day produced some inhibition of tumor growth, but no tumor-bearing mouse was cured. A single administration of CGP57148B caused substantial (>50%) but short-lived (2-5 h) inhibition of Bcr/Abl kinase activity. On the basis of the results from in vitro wash-out expts., 20-21 h was defined as the duration of continuous exposure needed to block cell proliferation and to induce apoptosis in these two leukemia cell lines. A treatment regimen assuring the continuous block of the Bcr/Abl phosphorylating activity that was administered over an 11-day period cured 87%-100% of treated mice. These data indicate that the continuous block of the oncogenic tyrosine kinase of Bcr/Abl protein is needed to produce important biol. effects in vivo.
IT **152459-95-5**, CGP57148B
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in vivo eradication of human BCR/ABL-pos. leukemia cells with an ABL kinase inhibitor)
RN 152459-95-5 CAPLUS

CN Benzamide, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]- (9CI) (CA INDEX NAME)



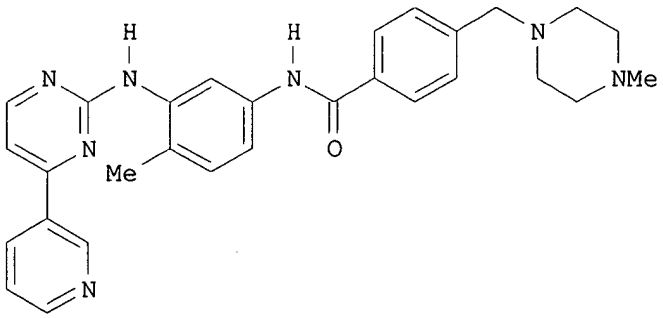
RE.CNT 11
RE
(1) Barila, D; Nat Genet 1998, V18, P280 CAPLUS
(2) Buchdunger, E; Cancer Res 1996, V56, P100 CAPLUS
(3) Deininger, M; Blood 1997, V90, P3691 CAPLUS
(4) Druker, B; Nat Med 1996, V2, P561 CAPLUS
(5) Gambacorti-Passerini, C; Blood Cells Mol Dis 1997, V23, P380 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> D BIB ABS HITSTR 10

L12 ANSWER 10 OF 21 CAPLUS COPYRIGHT 2000 ACS
AN 1999:77563 CAPLUS
DN 130:158400
TI Crystal modification of a N-phenyl-2-pyrimidineamine derivative, processes
for its manufacture and its use
IN Zimmermann, Jurg; Sutter, Bertrand; Burger, Hans Michael
PA Novartis A.-G., Switz.; Novartis-Erfindungen Verwaltungsgesellschaft m.b.H.
SO PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9903854	A1	19990128	WO 1998-EP4427	19980716
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 9889759	A1	19990210	AU 1998-89759	19980716
	EP 998473	A1	20000510	EP 1998-941342	19980716
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO				
	ZA 9806362	A	19990122	ZA 1998-6362	19980717
	NO 2000000227	A	20000117	NO 2000-227	20000117
PRAI	CH 1997-1764		19970718		
	WO 1998-EP4427		19980716		

GI

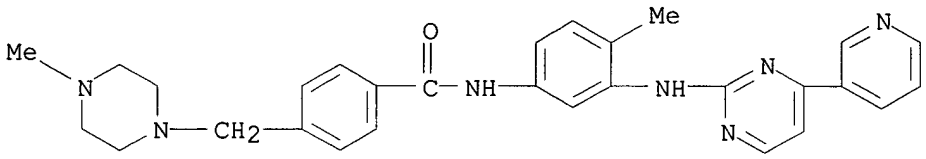


I

AB The invention relates to a new cryst. form of the methanesulfonic acid

addn. salt of I which may be used, for example, for tumor therapy. I was treated with methanesulfonic acid in MeOH to give the .alpha.-crystal form which in MeOH soln. is inoculated with a .beta.-crystal form to give the .beta.-variants. Tablets and capsules were prepd. contg. these crystal forms.

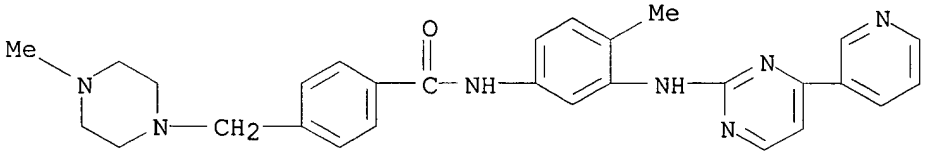
IT **152459-95-5**
RL: RCT (Reactant)
(salt formation of; crystal modification of a N-phenyl-2-pyrimidineamine deriv. for pharmaceuticals)
RN 152459-95-5 CAPLUS
CN Benzamide, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]- (9CI) (CA INDEX NAME)



IT **220127-57-1P**
RL: PEP (Physical, engineering or chemical process); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(.beta.-form; crystal modification of a N-phenyl-2-pyrimidineamine deriv. for pharmaceuticals)
RN 220127-57-1 CAPLUS
CN Benzamide, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-, monomethanesulfonate (9CI) (CA INDEX NAME)

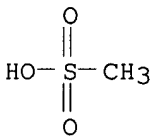
CM 1

CRN 152459-95-5
CMF C29 H31 N7 O



CM 2

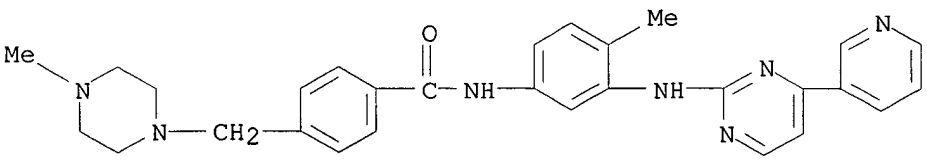
CRN 75-75-2
CMF C H4 O3 S



RE.CNT 1
RE
(1) Zimmermann, J; US 5521184 A 1996 CAPLUS

=> D BIB ABS HITSTR 11

L12 ANSWER 11 OF 21 CAPLUS COPYRIGHT 2000 ACS
AN 1998:571351 CAPLUS
DN 129:310547
TI Selective induction of apoptosis in Philadelphia chromosome-positive chronic myelogenous leukemia cells by an inhibitor of BCR-ABL tyrosine kinase, CGP 57148
AU Dan, Shingo; Naito, Mikihiko; Tsuruo, Takashi
CS Institute of Molecular and Cellular Biosciences, The University of Tokyo, Tokyo, Japan
SO Cell Death Differ. (1998), 5(8), 710-715
CODEN: CDDIEK; ISSN: 1350-9047
PB Stockton Press
DT Journal
LA English
AB The BCR -- ABL tyrosine kinase has been implicated as the cause of Philadelphia chromosome (Ph1)-pos. leukemias. The authors report herein that CGP 57148, a selective inhibitor of the ABL tyrosine kinase, caused apoptosis specifically in bcr -- abl-pos. chronic myelogenous leukemia (CML) cells, K562 and KYO-1. Upon treatment with CGP 57148, CRKL, a specific substrate for BCR -- ABL that propagates signals via phosphatidylinositol-3' kinase (PI3K), was dephosphorylated, indicating inhibition of BCR -- ABL tyrosine kinase at the cellular level. Likewise, MAPK/ERK, a downstream mediator of Ras, was also dephosphorylated. Caspase activation and cleavage of retinoblastoma protein (pRB) accompanied the development of CGP 57148-induced apoptosis. Inhibition of caspase suppressed apoptosis and the cleavage of pRB, and in turn arrested cells in the G1 phase. These results indicate that CGP 57148 shows apoptogenic and antiproliferative effects on bcr -- abl-pos. cells by blocking BCR -- ABL-initiated signaling pathways.
IT **152459-95-5**, CGP 57148
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(induction of apoptosis in Philadelphia chromosome-pos. CML cells by an inhibitor of BCR-ABL tk, CGP 57148)
RN 152459-95-5 CAPLUS
CN Benzamide, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]- (9CI) (CA INDEX NAME)



=> D BIB ABS HITSTR 12

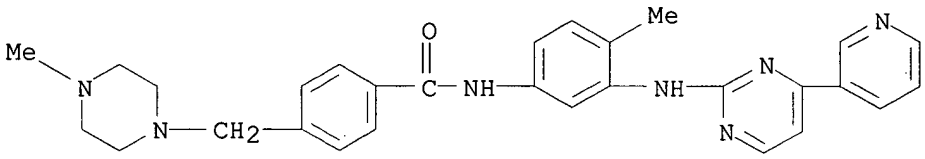
L12 ANSWER 12 OF 21 CAPLUS COPYRIGHT 2000 ACS
AN 1998:466156 CAPLUS
DN 129:239540
TI Selective inhibition of cell proliferation and BCR-ABL phosphorylation in acute lymphoblastic leukemia cells expressing Mr 190,000 BCR-ABL protein by a tyrosine kinase inhibitor (CGP-57148)
AU Beran, Miloslav; Cao, Xiaobo; Estrov, Zeev; Jeha, Sima; Jin, Guozhong; O'brien, Susan; Talpaz, Moshe; Arlinghaus, Ralph B.; Lydon, Nicholas B.; Kantarjian, Hagop
CS Leukemia Department, University of Texas M. D. Anderson Cancer Center, Houston, TX, 77030, USA
SO Clin. Cancer Res. (1998), 4(7), 1661-1672
CODEN: CCREF4; ISSN: 1078-0432
PB American Association for Cancer Research
DT Journal
LA English
AB The excessive proliferation of the myeloid marrow compartment in Philadelphia chromosome (Ph)-pos. acute and chronic leukemias has been largely attributed to a hyperactive and autonomously acting hybrid tyrosine kinase BCR-ABL, a product of the fusion between the second exon of the c-ABL proto-oncogene and 5' portions of the BCR gene on chromosome 22. This specific mol. event, amenable to attack with specifically designed inhibitors, has recently been successfully influenced by the drug CGP-57148 in mammalian cells transfected with full-length BCR-ABL gene and expressing full-length p210Bcr-Abl protein, as well as in primary human leukemic cells expressing p210Bcr-Abl fusion protein. In view of the heterogeneity of BCR-ABL transcripts assocd. with various phenotypes, we investigated the effect of CGP-57148 on p190Bcr-Abl- and p210Bcr-Abl-expressing, patient-derived cell lines and primary intact blast cells. In particular, we were interested in whether the variations in mol. events and/or the phenotype of Ph-pos. cells would affect their susceptibility to the specific tyrosine kinase inhibitor CGP-57148. We have demonstrated that the sensitivity of human cells with lymphoblastic immunophenotype expressing p190Bcr-Abl protein is comparable to that for leukemic myeloid cells expressing p210Bcr-Abl protein. After documenting profound and phenotype-independent suppression of both autophosphorylation and cell growth, we explored the importance of time and dose of exposure on the manifestation and stability of the induced events. Although there were variations between target cells, in vitro exposure for 24-48 h induced extensive and apparently irreversible apoptosis in BCR-ABL-expressing but not other normal or BCR-ABL-neg. leukemic cells. These findings support the potential use of CGP-57148 to purge Ph-pos. cells from autologous bone marrow in vitro. Another important finding was the comparable suppressive effect of temporary CGP-57148 exposure on both clonogenic KBM-5 cells and the whole cell population. Exposure time and dose appeared to be important variables among various cell types. Moreover, EDs appeared uniformly harmless to cells lacking BCR-ABL protein functioning as tyrosine kinase. Thus, the continuous exposure of target

cells, at least during the initial period of 24-48 h, may prove to be an important variable in the design of in vitro and in vivo therapy using tyrosine kinase inhibitors.

IT **152459-95-5**, CGP-57148
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(selective inhibition of cell proliferation and BCR-ABL phosphorylation
in acute lymphoblastic leukemia cells expressing Mr 190,000 BCR-ABL protein by tyrosine kinase inhibitor CGP-57148)

RN 152459-95-5 CAPLUS

CN Benzamide, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]- (9CI) (CA INDEX NAME)



=> D BIB ABS HITSTR 13

L12 ANSWER 13 OF 21 CAPLUS COPYRIGHT 2000 ACS
AN 1998:159344 CAPLUS
DN 128:265824
TI Inhibition of the ABL kinase activity blocks the proliferation of BCR/ABL+ leukemic cells and induces apoptosis
AU Gambacorti-Passerini, Carlo; Le Coutre, Philipp; Mologni, Luca; Fanelli, Mirco; Bertazzoli, Carla; Marchesi, Edoardo; Di Nicola, Massimo; Biondi, Andrea; Corneo, Gian Marco; Belotti, Daniela; Pogliani, Enrico; Lydon, Nicholas B.
CS Division of Experimental Oncology D and Medical Oncology C, Istituto Nazionale Tumori, Milan, 20133, Italy
SO Blood Cells, Mol. Dis. (1997), 23(3), 380-394
CODEN: BCMDFX; ISSN: 1079-9796
PB Academic Press
DT Journal
LA English
AB The BCR/ABL fusion protein transforms myeloid stem cells. Both chronic myelogenous leukemias (CML) and a subset of acute lymphoblastic leukemias (ALL) are assocd. with the expression of BCR/ABL proteins. This knowledge has not yet been translated into any specific tool to control ABL driven neoplastic cells growth. CGP57148B is an ATP-competitive inhibitor of the ABL protein kinase; it has been shown to inhibit the kinase activity of ABL both in vitro and in vivo and to inhibit the growth of v-abl and bcr/abl transfectants, as well as the in vitro formation of bone marrow (BM)-derived colonies in the presence of growth factors in some CML patients. These studies were performed to investigate the activity of CGP57148B on the spontaneous proliferation of both fresh and cultured, leukemic and normal, BCR/ABL pos. and neg. cells, and to study its mechanism of action. Six cell lines derived from BCR/ABL+ leukemias (K562, BV173, KCL22, KU812, MC3, LAMA84), thirteen BCR/ABL neg. lines, both neoplastic (KG1, SU-DHL-1, U937, Daudi, NB4, NB4.306) and derived from normal cells (PHA blasts, LAK, fibroblasts, LCL, renal epithelial cells, endothelial cells, CD34+ cells), and 14 fresh leukemic samples were tested using a tritiated thymidine uptake assay. The in vivo phosphorylation of the BCR/ABL protein was evaluated by western blot, while apoptosis was detected by the annexin V/propidium binding test. The induction of differentiation was assayed by immunofluorescence using multiple antibodies. All six BCR/ABL+ lines showed a dose dependent inhibition of their spontaneous proliferative rate, which was not accompanied by differentiation. The treatment caused, within minutes, dephosphorylation of the BCR/ABL protein, followed in 16-24 h by a decrease in cycling cells and induction of apoptosis. No significant inhibition of DNA synthesis was obsd. in any BCR/ABL neg. normal or neoplastic line at concns. .ltoreq.3 .mu.M, with the exception of fibroblasts and CD34 cells. Proliferation inhibition was obsd. also when using fresh samples obtained from two Ph+ ALL and 12 consecutive CML patients. Induction of apoptosis was obsd. in these samples too. The activity of CGP57148B can be monitored in ex vivo isolated or cultured

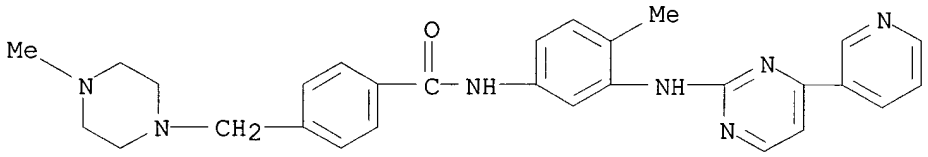
cells using a simple and reproducible assay, without the need for exogenously added growth factors. This mol. possibly exerts its effects through the inhibition of the kinase activity of BCR/ABL and the subsequent initiation of apoptosis, without inducing cell differentiation.

Some normal cells are also affected. These data support the use of CGP57148B in initial clin. studies; possible toxic effects on BM and fibroblast-derived cells will have to be closely monitored. The in vivo monitoring of patients will have to be focused on the induction of apoptosis in leukemic cells.

IT **152459-95-5**, CGP 57148B
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of ABL kinase activity blocks proliferation of BCR/ABL+ human leukemic cells and induces apoptosis)

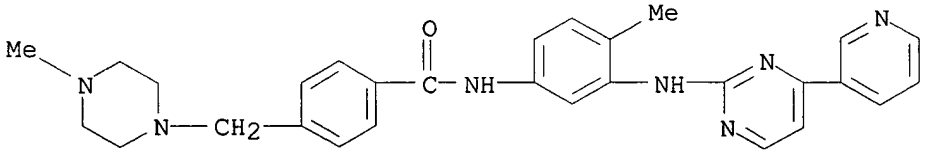
RN 152459-95-5 CAPLUS

CN Benzamide, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]- (9CI) (CA INDEX NAME)



=> D BIB ABS HITSTR 14

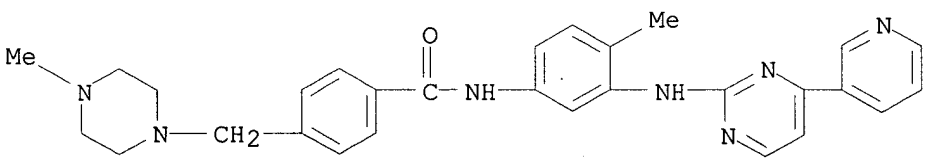
L12 ANSWER 14 OF 21 CAPLUS COPYRIGHT 2000 ACS
AN 1997:791751 CAPLUS
DN 128:110519
TI CGP 57148, a tyrosine kinase inhibitor, inhibits the growth of cells expressing BCR-ABL, TEL-ABL, and TEL-PDGFR fusion proteins
AU Carroll, Martin; Ohno-Jones, Sayuri; Tamura, Shu; Buchdunger, Elisabeth; Zimmermann, Jurg; Lydon, Nicholas B.; Gilliland, D. Gary; Druker, Brian J.
CS Division of Hematology and Medical Oncology, Oregon Health Sciences University, Portland, OR, 97201-3098, USA
SO Blood (1997), 90(12), 4947-4952
CODEN: BLOOAW; ISSN: 0006-4971
PB W. B. Saunders Co.
DT Journal
LA English
AB CGP 57148 is a compd. of the 2-phenylaminopyrimidine class that selectively inhibits the tyrosine kinase activity of the ABL and the platelet-derived growth factor receptor (PDGFR) protein tyrosine kinases. We previously showed that CGP 57148 selectively kills p210BCR-ABL-expressing cells. To extend these observations, we evaluated the ability of CGP 57148 to inhibit other activated ABL tyrosine kinases, including p185BCR-ABL and TEL-ABL. In cell-based assays of ABL tyrosine phosphorylation, inhibition of ABL kinase activity was obsd. at concns. similar to that reported for p210BCR-ABL. Consistent with the in vitro profile of this compd., the growth of cells expressing activated ABL protein tyrosine kinases was inhibited in the absence of exogenous growth factor. Growth inhibition was also obsd. with a p185BCR-ABL-pos. acute lymphocytic leukemia (ALL) cell line generated from a Philadelphia chromosome-pos. ALL patient. As CGP 57148 inhibits the PDGFR kinase, we also showed that cells expressing an activated PDGFR tyrosine kinase, TEL-PDGFR, are sensitive to this compd. Thus, this compd. may be useful for the treatment of a variety of BCR-ABL-pos. leukemias and for treatment of the subset of chronic myelomonocytic leukemia patients with a TEL-PDGFR fusion protein.
IT **152459-95-5**, CGP 57148
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of growth of cells expressing BCR-ABL, TEL-ABL, and TEL-PDGFR fusion proteins by tyrosine kinase inhibitor CGP 57148)
RN 152459-95-5 CAPLUS
CN Benzamide, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]- (9CI) (CA INDEX NAME)



Searched by John Dantzman 703-308-4488

=> D BIB ABS HITSTR 15

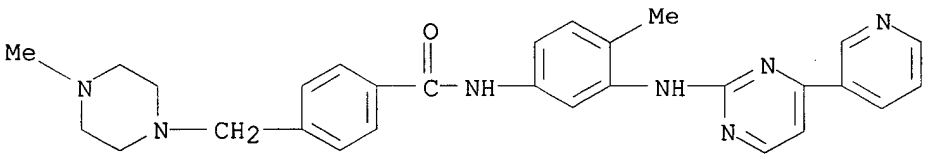
L12 ANSWER 15 OF 21 CAPLUS COPYRIGHT 2000 ACS
AN 1997:700998 CAPLUS
DN 128:57122
TI The tyrosine kinase inhibitor CGP57148B selectively inhibits the growth of BCR-ABL-positive cells
AU Deininger, Michael W. N.; Goldman, John M.; Lydon, Nicholas; Melo, Junia V.
CS Leukaemia Research Fund Centre for Adult Leukaemia, Department of Haematology, Royal Postgraduate Medical School, London, UK
SO Blood (1997), 90(9), 3691-3698
CODEN: BLOOAW; ISSN: 0006-4971
PB Saunders
DT Journal
LA English
AB The Philadelphia chromosome found in virtually all cases of chronic myeloid leukemia (CML) and in about one third of the cases of adult acute lymphoblastic leukemia is formed by a reciprocal translocation between chromosomes 9 and 22 that results in the fusion of BCR and ABL genetic sequences. This BCR-ABL hybrid gene codes for a fusion protein with deregulated tyrosine kinase activity that can apparently cause malignant transformation. CGP57148B, a 2-phenylaminopyrimidine deriv., has been shown to selectively inhibit the tyrosine kinase of ABL and BCR-ABL. We report here that this compd. selectively suppresses the growth of colony-forming unit-granulocyte/macrophage (CFU-GM) and burst-forming unit-erythroid derived from CML over a 2-logarithmic dose range with a maximal differential effect at 1.0 .mu.mol/L. However, almost all CML colonies that grow in the presence of 1.0 .mu.mol/L CGP57148B are BCR-ABL-pos., which may reflect the fact that residual normal clonogenic myeloid precursors are infrequent in most patients with CML. We also studied the effects of CGP57148B on hematopoietic cell lines. Proliferation was suppressed in most of the BCR-ABL-pos. lines; all five BCR-ABL-neg. lines were unaffected. We conclude that this new agent may have significant therapeutic applications.
IT **152459-95-5**, CGP 57148B
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tyrosine kinase inhibitor CGP57148B inhibition of growth of BCR-ABL-pos. cells)
RN 152459-95-5 CAPLUS
CN Benzamide, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]- (9CI) (CA INDEX NAME)



Searched by John Dantzman 703-308-4488

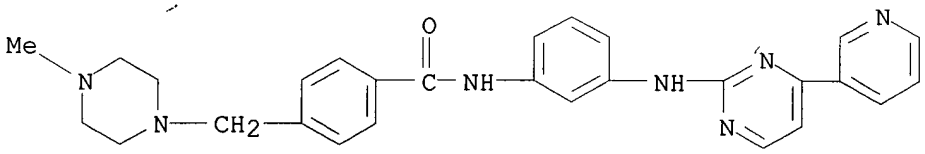
=> D BIB ABS HITSTR 16

L12 ANSWER 16 OF 21 CAPLUS COPYRIGHT 2000 ACS
AN 1997:305108 CAPLUS
DN 126:338243
TI Selective killing of BCR-ABL positive cells with a specific inhibitor of the ABL tyrosine kinase
AU Drucker, Brian J.; Ohno, Sayuri; Buchdunger, Elisabeth; Tamura, Shu; Zimmermann, Jurg; Lydon, Nicholas B.
CS Division of Hematology and Medical Oncology, Oregon Health Sciences University, Portland, OR, 97201, USA
SO Pezcoller Found. Symp. (1996), 7(Cancer Genes), 255-267
CODEN: PFSYES; ISSN: 0961-785X
PB Plenum
DT Journal; General Review
LA English
AB A review with 40 refs. on inhibition of chronic myelogenous leukemia with CGP 57148.
IT **152459-95-5**, CGP 57148
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(selective killing of BCR-ABL pos. cells with inhibitor of ABL tyrosine kinase)
RN 152459-95-5 CAPLUS
CN Benzamide, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]- (9CI) (CA INDEX NAME)

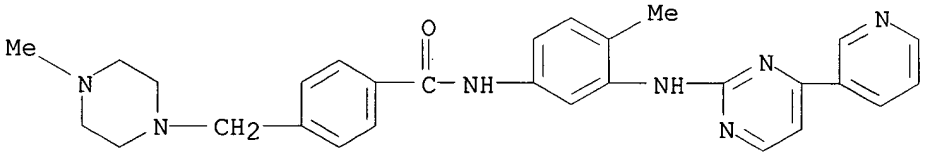


=> D BIB ABS HITSTR 17

L12 ANSWER 17 OF 21 CAPLUS COPYRIGHT 2000 ACS
AN 1997:123312 CAPLUS
DN 126:220297
TI Potent and selective inhibitors of the ABL-kinase: phenylaminopyrimidine (PAP) derivatives
AU Zimmermann, Jurg; Buchdunger, Elisabeth; Mett, Helmut; Meyer, Thomas; Lydon, Nicholas B.
CS Ciba Pharmaceuticals Division, Oncology Research Department, Ciba-Geigy Limited, Basel, CH-4002, Switz.
SO Bioorg. Med. Chem. Lett. (1997), 7(2), 187-192
CODEN: BMCLE8; ISSN: 0960-894X
PB Elsevier
DT Journal
LA English
AB Due to its relatively clear etiol., chronic myelogenous leukemia (CML) represents an ideal disease target for a therapy using a selective inhibitor of the Bcr-Abl tyrosine protein kinase. Extensive optimization of the class of phenylamino-pyrimidines yielded highly potent and selective Bcr-Abl kinase inhibitors.
IT **152459-93-3P 152459-95-5P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of phenylaminopyrimidine derivs. as inhibitors of ABL-kinase)
RN 152459-93-3 CAPLUS
CN Benzamide, 4-[(4-methyl-1-piperazinyl)methyl]-N-[3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]- (9CI) (CA INDEX NAME)



RN 152459-95-5 CAPLUS
CN Benzamide, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]- (9CI) (CA INDEX NAME)



Searched by John Dantzman 703-308-4488

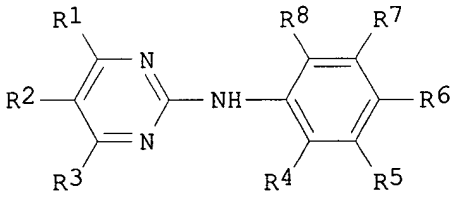
=> D BIB ABS HITSTR 18

L12 ANSWER 18 OF 21 CAPLUS COPYRIGHT 2000 ACS
AN 1996:380210 CAPLUS
DN 125:114681
TI Pyrimidine derivatives and processes for the preparation thereof
IN Zimmermann, Juerg
PA Ciba-Geigy Corporation, USA
SO U.S., 18 pp. Cont.-in-part of U.S. Ser. No. 42,322, abandoned.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5521184	A	19960528	US 1994-234889	19940428
	CA 2148477	AA	19950413	CA 1994-2148477	19940921
PRAI	CH 1992-1083	19920403			
	US 1993-42322	19930402			
	CH 1993-2966	19931001			

OS MARPAT 125:114681
GI

Provided

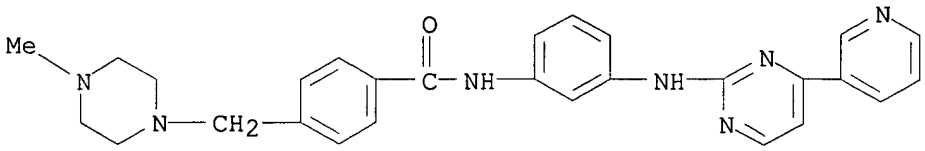


I

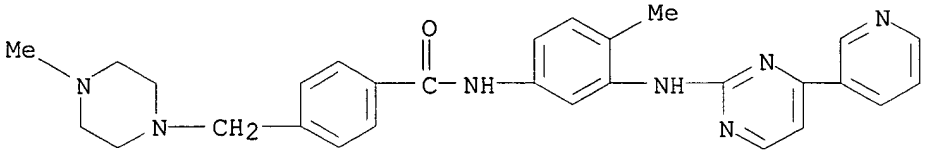
AB There are described N-phenyl-2-pyrimidine-amine derivs. (I) wherein R1 is 4-pyrazinyl, 1-methyl-1H-pyrrolyl, amino- or amino-lower alkyl-substituted Ph wherein the amino group in each case is free, alkylated or acylated, 1H-indolyl or 1H-imidazolyl bonded at a five-membered ring carbon atom, or unsubstituted or lower alkyl-substituted pyridyl bonded at a ring carbon atom and unsubstituted or substituted at the nitrogen atom by oxygen; R2 and R3 are hydrogen or lower alkyl; one or two of R4, R5, R6, R7 are each nitro, fluoro-substituted lower alkoxy or -N(R9)C(:X)(Y)nR10. These compds. can be used, for example, in the therapy of tumoral diseases. Three example formulations are given.

IT **152459-93-3P 152459-95-5P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of phenylaminopyrimidine derivs. as antitumor agents)

RN 152459-93-3 CAPLUS
CN Benzamide, 4-[(4-methyl-1-piperazinyl)methyl]-N-[3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]- (9CI) (CA INDEX NAME)

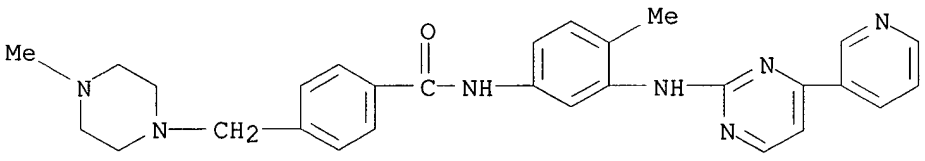


RN 152459-95-5 CAPLUS
CN Benzamide, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]- (9CI) (CA INDEX NAME)



=> D BIB ABS HITSTR 19

L12 ANSWER 19 OF 21 CAPLUS COPYRIGHT 2000 ACS
AN 1996:278213 CAPLUS
DN 125:453
TI Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells
AU Druker, Brian J.; Tamura, Shu; Buchdunger, Elisabeth; Ohno, Sayuri; Segal, Gerald M.; Fanning, Shane; Zimmermann, Jurg; Lydon, Nicholas B.
CS Division of Hematology and Medical Oncology, Oregon Health Sciences Univ., Portland, OR, USA
SO Nat. Med. (N. Y.) (1996), 2(5), 561-566
CODEN: NAMEFI; ISSN: 1078-8956
DT Journal
LA English
AB The Bcr-Abl oncogene, present in 95% of patients with chronic myelogenous leukemia (CML), has been implicated as the cause of this disease. A compd., designed to inhibit the Abl protein tyrosine kinase (CGP 57148), was evaluated for its effects on cells contg. the Bcr-Abl fusion protein. Cellular proliferation and tumor formation by Bcr-Abl-expressing cells were specifically inhibited by this compd. In colony-forming assays of peripheral blood or bone marrow from patients with CML, there was a 92-98% decrease in the no. of Bcr-Abl colonies formed but no inhibition of normal colony formation. This compd. may be useful in the treatment of Bcr-Abl-pos. leukemias.
IT **152459-95-5**, CGP 57148
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of a selective inhibitor of Abl tyrosine kinase (CGP 57148) on growth of Bcr-Abl pos. human and lab. animal leukemia cells)
RN 152459-95-5 CAPLUS
CN Benzamide, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]- (9CI) (CA INDEX NAME)

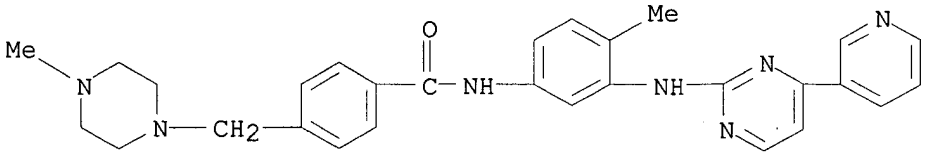


=> D BIB ABS HITSTR 20

L12 ANSWER 20 OF 21 CAPLUS COPYRIGHT 2000 ACS
AN 1996:22420 CAPLUS
DN 124:164458
TI Inhibition of the Abl protein-tyrosine kinase in vitro and in vivo by a 2-phenylaminopyrimidine derivative
AU Buchdunger, Elisabeth; Zimmermann, Juerg; Mett, Helmut; Meyer, Thomas; Mueller, Marcel; Druker, Brian J.; Lydon, Nicholas B.
CS Ciba Pharmaceuticals Division, Oncology Research Department, Ciba-Geigy Limited, Basel, CH-4002, Switz.
SO Cancer Res. (1996), 56(1), 100-4
CODEN: CNREA8; ISSN: 0008-5472
DT Journal
LA English
AB Oncogenic activation of Abl proteins due to structural modifications can occur as a result of viral transduction or chromosomal translocation. The tyrosine protein kinase activity of oncogenic Abl proteins is known to be essential for their transforming activity. Therefore, we have attempted to identify selective inhibitors of the Abl tyrosine protein kinase. Herein we describe an inhibitor (CGP 57148) of the Abl and platelet-derived growth factor (PDGF) receptor protein-tyrosine kinases from the 2-phenylaminopyrimidine class, which is highly active in vitro and in vivo. Submicromolar concns. of the compd. inhibited both v-Abl and PDGF receptor autophosphorylation and PDGF-induced c-fos mRNA expression selectively in intact cells. In contrast, ligand-induced growth factor receptor autophosphorylation in response to epidermal growth factor (EGF), insulin-like growth factor-I, and insulin showed no or weak inhibition by high concns. of CGP 57148. C-fos mRNA expression induced by EGF, fibroblast growth factor, or phorbol ester was also insensitive to inhibition by CGP 57148. In antiproliferative assays, the compd. was more than 30-100-fold more potent in inhibiting growth of v-abl-transformed PB-3c cells and v-sis-transformed BALB/c 3T3 cells relative to inhibition of EGF-dependent BaLB/MK cells, interleukin-3-dependent FDC-P1 cells, and the T24 bladder carcinoma line. Furthermore, anchorage-independent growth of v-abl- and v-sis-transformed BALB/c 3T3 cells was inhibited potently by CGP 57148. When tested in vivo, CGP 57148 showed antitumor activity at tolerated doses against tumorigenic v-Abl- and v-sis-transformed BALB/c 3T3 cells. In contrast, CGP 57148 had no antitumor activity when tested using src-transformed BALB/c 3T3 cells. These findings suggest that CGP 57148 may have therapeutic potential for the treatment of diseases that involve abnormal cellular proliferation induced by Abl protein-tyrosine kinase deregulation or PDGF receptor activation.
IT **152459-95-5**, CGP 57148
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in treatment of diseases that involve abnormal cellular proliferation induced by Abl protein-tyrosine kinase deregulation or PDGF receptor activation)

Searched by John Dantzman 703-308-4488

RN 152459-95-5 CAPLUS
CN Benzamide, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]- (9CI) (CA INDEX NAME)

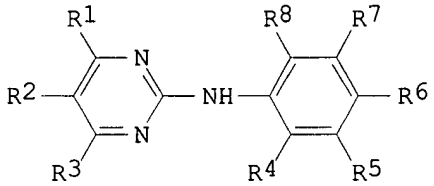


=> D BIB ABS HITSTR 21

L12 ANSWER 21 OF 21 CAPLUS COPYRIGHT 2000 ACS
AN 1994:107056 CAPLUS
DN 120:107056
TI Preparation of 2-anilinopyrimidines as antiatherosclerotics and neoplasm inhibitors
IN Zimmermann, Juerg
PA Ciba-Geigy A.-G., Switz.
SO Eur. Pat. Appl., 23 pp.
CODEN: EPXXDW
DT Patent
LA German
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 564409	A1	19931006	EP 1993-810219	19930325
	EP 564409	B1	20000119		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
	AT 188964	E	20000215	AT 1993-810219	19930325
	CA 2093203	AA	19931004	CA 1993-2093203	19930401
	CZ 283944	B6	19980715	CZ 1993-560	19930401
	RU 2125992	C1	19990210	RU 1993-5357	19930401
	IL 105264	A1	19990411	IL 1993-105264	19930401
	NO 9301283	A	19931004	NO 1993-1283	19930402
	ZA 9302397	A	19931004	ZA 1993-2397	19930402
	AU 9335694	A1	19931007	AU 1993-35694	19930402
	AU 666709	B2	19960222		
	CN 1077713	A	19931027	CN 1993-103566	19930402
	CN 1043531	B	19990602		
	HU 64050	A2	19931129	HU 1993-982	19930402
	JP 06087834	A2	19940329	JP 1993-78096	19930405
	JP 2706682	B2	19980128		
PRAI	CH 1992-1083		19920403		

OS MARPAT 120:107056
GI



I

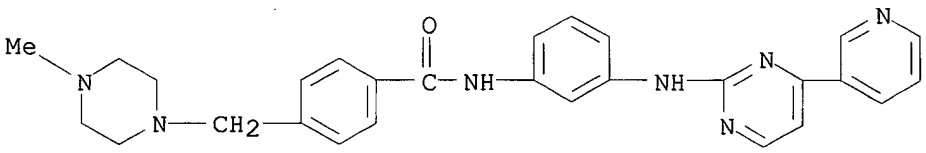
AB Title compds. [I; R1 = pyridyl, 4-pyrazinyl, (acyl)aminophenyl, etc.; R2, R3 = H, alkyl; 1 or 2 of R4-R8 = NO2, fluoroalkoxy, NR9C(:X)YnR10 and the others = H, alkyl, alkanoyl, CF3, etc.; R9 = H, alkyl; R10 = (cyclo)aliph. group, heterocyclyl, aryl, etc.; X = O, S, NH, etc.; Y = O or NH; n = 0 or 1] were prepd. Thus, 3-(O2N)C6H4NHC(:NH)NH2 [prepn. from 3-(O2N)C6H4NH2

provided

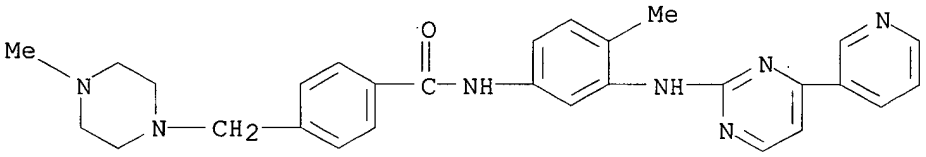
given] was cyclocondensed with R1COCH:CHNMe2 (R1 = 3-pyridyl) (prepn. from 3-acetylpyridine given) to give I (R1 = 3-pyridyl, R2 = R3 = R5-R8 = H, R4 = NO2). I had IC50 of .apprx.0.5 to 5 .mu.M against protein kinase C in vitro.

IT **152459-93-3P 152459-95-5P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as antiatherosclerotic and neoplasm inhibitor)

RN 152459-93-3 CAPLUS
CN Benzamide, 4-[(4-methyl-1-piperazinyl)methyl]-N-[3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]- (9CI) (CA INDEX NAME)

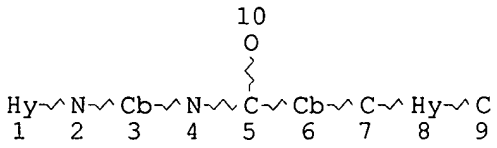


RN 152459-95-5 CAPLUS
CN Benzamide, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]- (9CI) (CA INDEX NAME)



=> D QUE L14

L9 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED
ECOUNT IS E4 C E2 N AT 1
ECOUNT IS E4 C E2 N AT 8

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 10

STEREO ATTRIBUTES: NONE
L14 QUE ABB=ON PLU=ON L9

=> D

L17 ANSWER 1 OF 2 COPYRIGHT 2000 BEILSTEIN CDS MDL

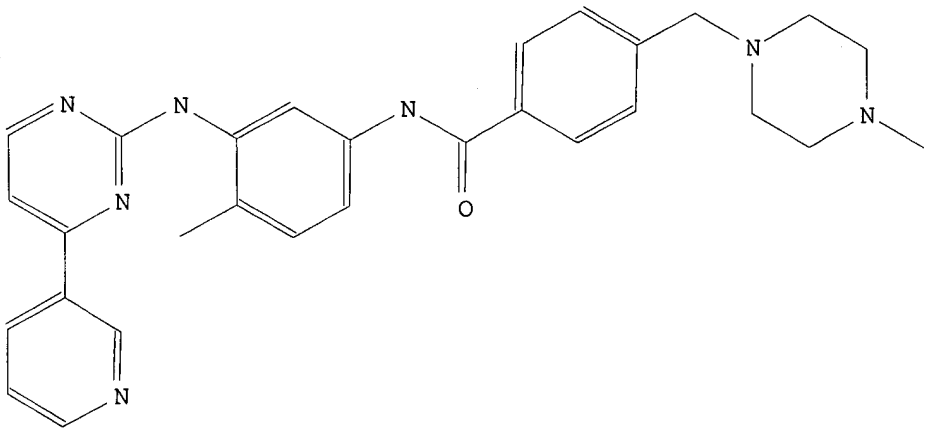
Beilstein Reg. No. (BRN): 7671333 Beilstein
Molecular Formula (MF): C29 H31 N7 O
Autonom Name (AUN):
4-(4-methyl-piperazin-1-ylmethyl)-N-<4-methyl-3-(4-

pyridin-3-yl-pyrimidin-2-ylamino)-phenyl>-benzamide
Beilstein Reference (SO): 6-26
Formula Weight (FW): 493.61
Lawson Number (LN): 30308; 28000; 16047; 14518; 2817

Ring System Data:

Number of Rings (CNR): 5
Ring Systems (CNRS): 5
Diff. Ring Systems (CNDRS): 4
Ring Heteros (CNRH): 5
Acyclic Heteros (CNAH): 3

Beilstein Ring Index (BRIX)	Ring System Formula (RF)	BRIX Count
6.1.0-0.0-3.1	C6	2
6.1.0-2.3-3.1	C4N2	1
6.1.0-1.1-3.1	C5N	1
6.1.0-2.2-0.0	C4N2	1



Preparation:
PRE

Searched by John Dantzman 703-308-4488

Start: BRN=7539016 N-(3-amino-phenyl)-4-(3-pyridyl)-2-pyrimidinamine,
BRN=7638629 4-(4-methyl-piperazin-1-ylmethyl)-benzoyl chloride
Reference(s):
1. Zimmermann, Juerg; Buchdunger, Elisabeth; Mett, Helmut; Meyer, Thomas; Lydon, Nicholas B., Bioorg.Med.Chem.Lett., 7 <1997> 2, 187-192, LA: EN,
CODEN: BMCLE8

See

=> D 2

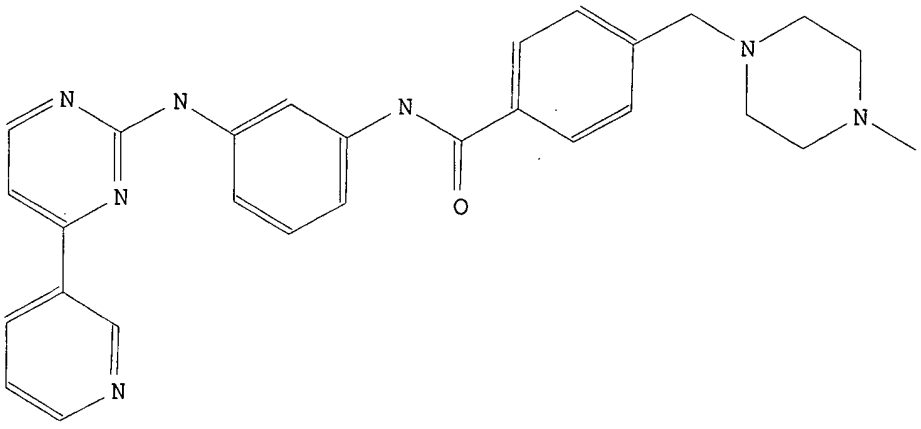
L17 ANSWER 2 OF 2 COPYRIGHT 2000 BEILSTEIN CDS MDL

Beilstein Reg. No. (BRN): 7669878 Beilstein
Molecular Formula (MF): C28 H29 N7 O
Autonom Name (AUN):
4-(4-methyl-piperazin-1-ylmethyl)-N-<3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl>-benzamide
Beilstein Reference (SO): 6-26
Formula Weight (FW): 479.58
Lawson Number (LN): 30308; 28000; 16047; 14508; 2817

Ring System Data:

Number of Rings (CNR): 5
Ring Systems (CNRS): 5
Diff. Ring Systems (CNDRS): 4
Ring Heteros (CNRH): 5
Acyclic Heteros (CNAH): 3

Beilstein Ring Index (BRIX)	Ring System Formula (RF)	BRIX Count
6.1.0-2.3-3.1	C4N2	1
6.1.0-1.1-3.1	C5N	1
6.1.0-0.0-3.1	C6	2
6.1.0-2.2-0.0	C4N2	1



Preparation:
PRE
Start: BRN=7536420
N-(4-pyridin-3-yl-pyrimidin-2-yl)-benzene-1,3-diamine
Prepared by Johnen, Dannemann, 1988, 4488

BRN=7638629 4-(4-methyl-piperazin-1-ylmethyl)-benzoyl chloride

Reference(s):

1. Zimmermann, Juerg; Buchdunger, Elisabeth; Mett, Helmut; Meyer, Thomas; Lydon, Nicholas B., Bioorg.Med.Chem.Lett., 7 <1997> 2, 187-192, LA: EN,

CODEN: BMCLE8